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ENGAGEMENT IN CARE DURING ACTIVE DUTY HIV TREATMENT

by

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June 2017

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Human immunodeficiency virus (HIV) infection is a serious illness that affects individuals, including military personnel, all over the world. If left unchecked, HIV has dangerous implications for a patient's immune health, eventually progressing to Acquired Immunodeficiency Syndrome (AIDS). The purpose of this analysis was to determine how effective the U.S. military is at reaching 90% viral suppression in its HIV-positive service members. The main goal was to determine which factors contribute to reaching viral suppression. Using Kaplan-Meier survival function estimates and Cox proportional hazards models it was determined that service members who initiated treatment under more inclusive policies were more likely to reach viral suppression. The probability of viral suppression between services (Army, Navy, Air Force, and Marine Corps) was not significantly different. Identifying the factors that are important to reaching viral suppression in a closed military population may prove to be beneficial in understanding the limits of HIV transmission and its elimination through early treatment

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ENGAGEMENT IN CARE DURING ACTIVE DUTY HIV TREATMENT

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ABSTRACT

Human immunodeficiency virus (HIV) infection is a serious illness that affects individuals, including military personnel, all over the world. If left unchecked, HIV has dangerous implications for a patient's immune health, eventually progressing to Acquired Immunodeficiency Syndrome (AIDS). The purpose of this analysis was to determine how effective the U.S. military is at reaching 90% viral suppression in its HIV-positive service members. The main goal was to determine which factors contribute to reaching viral suppression. Using Kaplan-Meier survival function estimates and Cox proportional hazards models it was determined that service members who initiated treatment under more inclusive policies were more likely to reach viral suppression. The probability of viral suppression between services (Army, Navy, Air Force, and Marine Corps) was not significantly different. Identifying the factors that are important to reaching viral suppression in a closed military population may prove to be beneficial in understanding the limits of HIV transmission and its elimination through early treatment.

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LIST OF ACRONYMS AND ABBREVIATIONS

AFI	Air Force Instruction
AIDS	Acquired Immunodeficiency Syndrome
AR	Army Regulation
ART	antiretroviral therapy
CD4	disease fighting cell of the human immune system
CD8	similar to CD4
CDC	Center for Disease Control and Prevention
CDF	cumulative distribution function
HAART	highly active antiretroviral therapy
HIV	Human Immunodeficiency Virus
HST	Health Systems Trust
IDCRP	Infectious Disease Clinical Research Program
NIH	National Institute of Health
NHS	U.S. Military HIV Natural History Study
NMCPHC	Navy and Marine-Corps Public Health Center
PCS	permanent change of station
SANDF	South African National Defense Force
SECAF	Secretary of the Air Force
STI	sexually transmitted infection
SECNAVINST	Secretary of the Navy Instruction
UCSF	University of California, San Francisco
UNAIDS	Joint United Nations Programme on HIV/AIDS
VL	Viral load
WHO	World Health Organization

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EXECUTIVE SUMMARY

Human immunodeficiency virus (HIV) infection is a serious illness, which, if left unchecked, has dangerous implications for a patient's immune health, eventually progressing to Acquired Immunodeficiency Syndrome (AIDS). According to recent surveys, the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that as of 2015, almost 37 million people are living with HIV, and over two million people were newly infected with HIV in that year (UNAIDS 2015). UNAIDS has provided guidance on goals for ending the AIDS epidemic worldwide. Its most recent guidance is a program called "90–90-90." In short, the three 90s in the 90-90-90 program stand for the following: of those individuals infected, 90% shall know their HIV positive status; of those diagnosed, 90% shall be engaged in highly active antiretroviral therapy (HAART)—the standard treatment for HIV; and of those treated, 90% shall reach viral suppression (where the concentration of virus in the blood is so small it decreases the chance of passing on the infection). The basis for their strategy is the belief that "it will be impossible to end the epidemic without bringing HIV treatment to all who need it" (UNAIDS 2014). Mathematical models have suggested that if the targets of the 90-90-90 program are reached by 2020, the AIDS epidemic will come to a close by 2035 (UNAIDS 2014). In addition to viral load (the measure by which clinicians determine viral suppression), another indicator of an HIV-infected person's immune system is CD4, a white blood cell which is specifically targeted by HIV. Together, these indicators have historically been used to identify disease progression and when to initiate HAART.

The U.S. military provides a unique study population to help inform policy regarding the 90–90-90 target. While some studies on engagement in care have been conducted on populations in sub-Saharan Africa (Mwesigire et al. 2015), there are no in-depth studies of how all 3 targets are approached in the U.S. military, and how successful these efforts have been thus far. The U.S. military has already met the first 90, as all military personnel are tested regularly for HIV infection. The military has also met the second 90, as over 90% of patients are regularly engaged and adherent to their HAART regimen. Regarding the third 90, viral suppression, CD4, and viral load data are regularly

collected in an active surveillance program for all HIV positive service members in an open cohort. As such, from these data it can be determined how successful the current military engagement policies are at helping service members achieve viral suppression (Infectious Disease Clinical Research Program (ICDRP) 2015).

The objective of this research is to answer questions about the effectiveness of U.S. military policies regarding care for HIV positive service members. Specifically, questions will be answered regarding the percentage of HIV positive patients who initiate antiretroviral therapy (ART), and what percentage of those who initiate ART achieve viral suppression. Services will initially be analyzed separately to see if there are differences in terms of engagement between them. Other factors will be evaluated to determine their effect, if any, on treatment engagement, to include demographics, therapeutic methods, and specific policies.

The two main methods that will be used in this analysis are Kaplan-Meier estimates and Cox proportional hazards models. We set all starting times for each patient to $t = 0$, giving each patient the same starting point, and treating the population as if they move forward in time together. One of three things can happen to patients in these estimates: the patient can run out of clinical data before the full time period of the analysis is up (for unknown reasons); he or she can reach the outcome of interest (attaining a state of viral suppression); or the patient can continue to the end of the time period with neither event happening (survival). For each time period, the number of patients with available data for that time period (*n.risk)* and the number of those patients who achieve viral suppression (*n.event)* form a fraction estimating the likelihood a patient survives past that point in the cohort (i.e., does NOT achieve viral suppression), given that they have survived up to this time. This proportion is used for estimating the overall survival function of the patients in the cohort.

Cox proportional hazards models allow us to look at all factors in a dataset, and see how relevant each is to the survival of patients, including interactions between the variables. It behaves much like a generalized linear model (glm) with $\boldsymbol{\beta}$ being a vector of coefficients corresponding to the covariates included in the model (Therneau 2015).

Survival functions for the time to viral suppression were estimated for a number of different factors, including service, treatment policy, baseline CD4 at treatment initiation, and PCS. There was no appreciable difference between the services. The most inclusive treatment policy, which allowed patients to start treatment earliest, showed the most positive results. Those patients whose baseline CD4 at treatment initiation was at least 500 showed much improvement over those who were less healthy (lower CD4 counts). As shown in Figure 1, those individuals who were part of the most inclusive treatment group were more likely to reach viral suppression earlier.

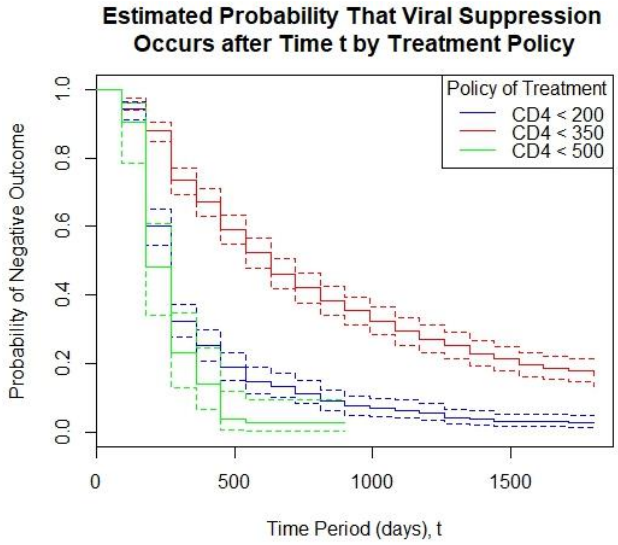

Figure 1. Estimated Survival Function by Treatment Policy

The trends shown in Figure 1 show decreased time to reach viral suppression with more inclusive care

A secondary aim of this analysis was to determine the percent of the cohort that reaches viral suppression. As shown in Figure 2, the treated cohort reached well over 90% cumulative probability of viral suppression by the end of the observed time frame.

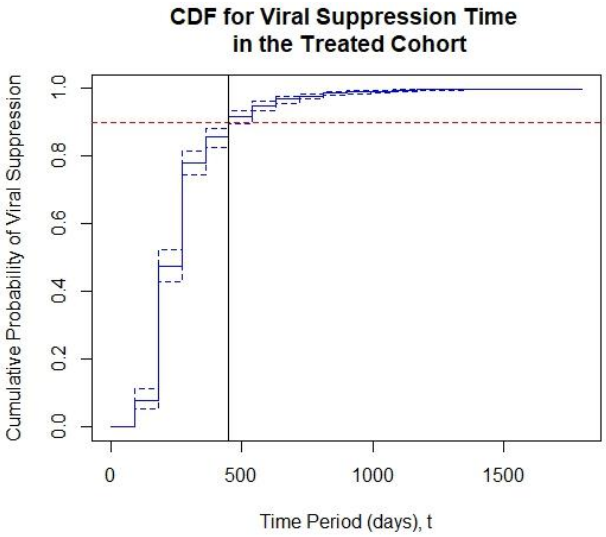

Figure 2. Estimated Probability of the Treated Cohort Reaching Viral Suppression in Each Time Step

Overall, without even taking into account time, changes in treatment guidelines, or the many other factors in this analysis, the treated military cohort achieved about 99% cumulative probability of viral suppression in this 5-year study window. The estimated cumulative probability that the treated cohort reached viral suppression passed 90% at time t = 450 days.

Next, Cox proportional hazards models were examined to determine how these factors contributed when placed into a model together. In the final Cox proportional hazards model, we found that enlisted personnel did significantly worse than officers (p value = 0.004), and were about 25% less likely to reach viral suppression than officers were. Those without an applicable rank did slightly better than officers (p value = 0.052) and were about 60% more likely to reach viral suppression. Being treated increased an individual's chances of viral suppression significantly (p value = 0.000). Having a baseline CD4 between 200 and 349 did not significantly increase an individual's chances of viral suppression compared to those with baseline CD4 less than 200 (p value = 0.520). Those with a baseline CD4 between 350 and 500 were also not significantly different (p value = 0.349). Those individuals who had a baseline CD4 above 500 were almost 30% more likely to reach viral suppression than those with a baseline CD4 less than 200 (Estimated Hazard Ratio = 1.172, 95% C.I. (0.916, 1.497)). Those in the

medium inclusive treatment policy were 80% more likely to reach viral suppression than the most restrictive policy (p value = 0.000). Those in the least restrictive policy did as well, being almost 80% more likely to reach viral suppression than the most restrictive policy, but this improvement was not significant at the 5% level of significance.

In conclusion, no appreciable difference can be noted between the services. However, many important differences were found between the treatment policies, baseline CD4 levels, and time of treatment. These results corroborate what UNAIDS has put out in guidance, that early initiation of ART, regardless of CD4 count, as well as continuity of care, is essential to achieving a positive outcome for the patient (UNAIDS 2014).

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I. INTRODUCTION

A. PROLOGUE

Human immunodeficiency virus (HIV) infection is a serious illness, which, if left unchecked, has dangerous implications for a patient's immune health, eventually progressing to Acquired Immunodeficiency Syndrome (AIDS). Two main metrics are used to assess the state of the HIV/AIDS epidemic: prevalence and incidence. Prevalence is defined as what percentage of the study population has the disease (Center for Disease Control and Prevention (CDC) 2016a). Incidence is defined as the number of new infections every year. However, incidence is much harder to measure, as it is difficult to differentiate delayed diagnoses, which are accounted for in the prevalence estimate, from the truly new cases (CDC 2016a). Since incidence of new infections contributes to the prevalence in a population, it is likely the decline in prevalence of cases would be preceded by a decline in incidence (Joint United Nations Programme on HIV/AIDS (UNAIDS) 1999). According to recent surveys, UNAIDS estimates that in 2015, almost 37 million people were living with HIV (prevalence) and over two million people were newly infected with HIV in that year (incidence) (UNAIDS 2015)

The Joint United Nations Programme on HIV/AIDS has provided guidance on goals for ending the AIDS epidemic worldwide. Its most recent guidance is a program called "90–90-90." The basis for their strategy is the belief that "it will be impossible to end the epidemic without bringing HIV treatment to all who need it" (UNAIDS 2014). Mathematical models have suggested that if the targets of the 90-90-90 program are reached by 2020, the AIDS epidemic will end by 2035 (UNAIDS 2014). An important part of the program is to identify populations among whom the disease is more likely to be transmitted. These groups are known as "at-risk populations" (UNAIDS 2014). In identification of at-risk populations, the incidence measure can shed light on where prevention efforts can be most effective. For example, in 2015, the highest rate of newly identified infections was in individuals ages 25 to 29, and 70% of new cases identified male-to-male sexual contact and/or injection drug-use as the mode of transmission (CDC

2016a). These data can provide important information for targeting both testing and information campaigns.

The first 90 in the 90-90-90 program stands for the goal of having 90% of HIV positive individuals know their status (UNAIDS 2014). To achieve this by 2020, a much more active role must be taken in testing. Currently, in many communities, the patient must request HIV tests. This requires the patient to realize they are at risk and seek out verification for themselves. This can be problematic, especially in regions or communities that are not properly educated about testing and risk factors for HIV transmission (UNAIDS 2014). As such, more strategic targeting of at-risk populations must be done, and much more proactively than it has been previously.

Once identified, individuals infected with HIV must take an active role in ensuring their continued health and survival. This means staying active in what is known as the cascade of treatment, also known as the care continuum, or cascade of care. The cascade of treatment includes testing and knowing one's HIV status, beginning medical treatment, continued engagement in care, and ends with viral suppression (CDC 2016b). Engagement in care means receiving care for HIV, and viral suppression means achieving an extremely low number of active copies of the virus in the patient (CDC 2016b).

The second 90 stands for 90% of those diagnosed with HIV will receive sustained antiretroviral therapy (ART). The most current version of ART is Highly Active antiretroviral therapy (HAART). HAART has been shown to reduce the percentage of AIDS outcomes among patients (Cain et al. 2009). In fact, treatment with ART has also been shown to decrease risk of transmission between couples where one partner is positive, but the other is uninfected. In other words, if the HIV positive partner is treated with ART, they are much less likely to pass the virus on to their partner (Anglemyer et al. 2013). This treatment provides compelling evidence that it is more effective than previous methods and can help UNAIDS reach its 90–90-90 goal by 2020. However, even though HAART may be a more effective treatment, actual sustained treatment is still difficult. According to UNAIDS: "ending AIDS will require uninterrupted access to lifelong treatment for tens of millions of people" (UNAIDS 2014). This requires a more

flexible and affordable infrastructure than the current system. Increasing the affordability, probability of success, and time needed between treatments can all aid in this effort (UNAIDS 2014). In areas of high infection, and low economic means, this almost always means the treatment must be free to the individual.

The most common ways to monitor the success of treatment are to use CD4 counts and viral load. CD4 is a measure of how strong the immune system is, with higher numbers being related to better health or a slower progression of the disease (CDC 2016a). Viral load is the measure of the number of active copies of the virus in the body, with lower numbers related to better health (CDC 2016a). For the purposes of this study, increased CD4 counts and decreased viral load are considered indications of improved health in the patient.

The third 90 represents 90% of people who receive ART go into viral suppression. Viral suppression means the virus is in such small concentration in the host that its effects are negligible and manageable. Viral suppression is a key stage in HIV positive patients because it opens up other possible medical procedures, and reduces the risk of transmission. Currently, for an HIV positive patient to be eligible for an organ transplant, they must either have a CD4 count above 200, or be in a stage of viral suppression (University of California, San Francisco (UCSF) 2013). Advances in ART show that, in the Latin-American countries, "80% of individuals receiving antiretroviral therapy … achieved viral suppression" (UNAIDS 2014). While this statistic makes it seem that the third 90 is already within reach, many such statistics do not account for mortality or attrition from the cascade of treatment. Achieving this target requires providers to put more effort into tracking and retaining their patients, and demands patients adhere to their regimens and stay engaged in the cascade of treatment (UNAIDS 2014).

90-90-90, while certainly an ambitious program, is not an impossible one. In fact, if 90-90-90 is achieved by 2020, UNAIDS predicts the AIDS epidemic will come to a close by 2035 (UNAIDS 2014). Just in the past few years, significant progress has been made in several different countries toward meeting the 2020 deadline. In Botswana, recent efforts to meet the 90–90-90 target resulted in 70.2% of HIV positive patients

achieving viral suppression (UNAIDS 2016). In fact, "new evidence in 2016 indicates that Sweden has already achieved 90–90-90" (UNAIDS 2016). While Sweden is currently the only country with documented evidence of meeting the 90–90-90 target, other populations are fast approaching the same goal.

Ending the HIV epidemic worldwide carries extraordinary significance. Everybody would argue that healthier populations are beneficial to a society. Furthermore, in the context of national security, an HIV-negative military underscores not only the importance of healthier populations, but also highlights the strategic implications the implementation of 90–90-90 targets could have. In this thesis, we analyze how close the United States military is to achieving 90-90-90, and what factors have the strongest impacts on meeting these targets.

B. BACKGROUND

The U.S. military provides a unique study population to help inform policy regarding the 90–90-90 target. While some studies on engagement in care have been conducted on military and civilian populations in sub-Saharan Africa (Mwesigire et al. 2015), there are no in-depth studies of how all 3 targets are approached in the U.S. military, and how successful these efforts have been thus far.

The at-risk population for the military shares many of the same characteristics as the U.S. population at large. While 70% of the incident cases in the civilian population are from male-to-male sexual contact or injection drug use (CDC 2016a), the U.S. Navy asserts that 82% of males with HIV are infected by male-to-male sexual contact, with only 5% transmission from injection drug use (Navy and Marine Corps Public Health Center (NMCPHC) 2016a). This is to be expected, given the U.S. military's zero tolerance stance on drug-use. The highest risk among demographics is among African Americans in both the U.S. Navy and the general population in the U.S. (CDC 2016a, NMCPHC 2016a).

The U.S. military is also unique in that all active duty and Reserve members are screened for HIV regularly. Once every two years, every single active duty service member is tested for HIV (Infectious Disease Clinical Research Program (IDCRP)

2015a). Their positive or negative status is reported to them and their healthcare providers as soon as it is known (NMCPHC 2016a). As such, the first 90 target is already met (and surpassed) in the U.S. military, as 100% of active duty service members are tested and aware of their HIV status. In fact, initial screening for HIV is done before civilians enter service, so this testing also makes some members outside the military aware of their HIV status as well. With this important target in the 90–90-90 goal already reached, it is possible to look more closely at the next two.

The military stands on good footing to achieve the second 90: initiation of ART. All service members have access to free healthcare, and receive regular checkups, at minimum, once every year, to evaluate their overall health. Per Department of Defense Instruction (DoDI) 6025.19, these checkups are mandated, and each command ensures its service members are making use of these services as needed (Department of Defense (DOD) 2014). As previously mentioned, free access to ART and regular engagement in care is key to achieving viral suppression. This potentially high rate of ART initiation among HIV-infected service members indicates that the second 90 target has already been met.

Regarding the third 90, viral suppression, CD4 count and viral load data are regularly collected in an active surveillance program for all HIV positive service members in an open cohort. As such, from these data, it can be determined how successful the current military engagement policies are at helping service members achieve viral suppression (ICDRP 2015b).

C. OVERVIEW

This study uses the largest repository of active duty military HIV infection data in existence. The cohort, since its establishment in 1986, has enrolled nearly 6,000 active duty members, and has over 1,500 active participants (IDCRP 2015a). The current dataset contains multiple visit data for each patient, and recorded CD4 counts and viral load measurements and, when available, outcome results.

The population of interest includes all members of the current cohort, which includes active duty service members and any of their beneficiaries who are infected with

HIV. The longest record in the current dataset spans over 3,700 days. Demographic data, as well as engagement and clinical information, are available for the participants, of which, the clinical data are identified by date.

D. PROBLEM STATEMENT

HIV infection is a serious concern of the U.S. military. Air Force Instruction (AFI) 44–178 mandates that HIV positive service members must have constant access to treatment and care (Secretary of the Air Force [SECAF] 2014). In the Department of the Navy alone, an active duty sailor or Marine is infected with HIV about once every 4 days (NMCPHC 2016b). Most of the time, the service members are allowed to remain on active duty, unless their health deteriorates to where they can no longer perform their duties. However, enlisted service members who have tested HIV positive while in service lose access to commissioning programs (NMCPHC 2016a), robbing the military of potential officers, and limiting career flexibility of promising individuals.

As late as 2010, HIV policy prohibited HIV positive service members from being assigned to deployable units (NMCPHC 2010). This policy was recently changed to allow those HIV positive members in good health to be assigned to operational units (NMCPHC 2016b). However, this is on a case-by-case basis, and depends entirely on how healthy the service member is. As such, engagement in care and viral suppression are key to maintaining operational effectiveness and retention of qualified service members.

Thomas et. al. (2014) studied military populations in sub-Saharan Africa and found that all HIV positive service members seroconverted (became HIV positive) after entering the service. The authors found that most countries allowed their HIV positive members to be deployed overseas, and required regular testing of active duty members for HIV. However, another study of data from the South African National Defense Force (SANDF) revealed that the South African military is losing at least 400,000 working days a year due to HIV infection (Health Systems Trust (HST) 2004). While the U.S. military is not in as serious a predicament, HIV infection poses a risk to operational availability and readiness.

E. OBJECTIVE

The objective of this research is to answer questions about the effectiveness of U.S. military policies regarding care for HIV positive service members. Specifically, questions will be answered regarding the percentage of HIV positive patients who initiate ART, the frequency of gaps in treatment, and what percentage of those who initiate ART achieve viral suppression. Services will be analyzed individually to see if viral suppression differs between them. Other factors will be observed to determine their effect, if any, on frequencies of engagement, to include demographics and specific policies.

F. SCOPE AND OUTLINE

The data used in this thesis are from the "U.S. Military HIV Natural History Study" (NHS), and include HIV cases of active duty military and their infected dependents from 2008 to 2015. The prospective cohort that will be used to answer these research questions is drawn from this population. Included in this cohort are active duty service members enrolled from 2008 to 2015, excluding subjects with less than one year of follow up (IDCRP 2015a).

This thesis analyzes the engagement in HIV care in the U.S. military population, with a particular focus on the differences in care between services, to include centralization of models of care, and demographic or operational differences. The cascade of engagement defined in this study includes infection, diagnosis, linkage to care, retention in care, initiation of ART, and viral suppression. The main outcome variable will be viral suppression. The two main tools used will be survival analysis with Kaplan-Meier and Cox proportional hazards models (Diez 2013).

Chapter II gives a detailed introduction to the current military policies, the study cohort, prior analyses, and the statistical methods used in this thesis. Chapter III describes the data and methods of analysis used, as well as some brief descriptive statistics. Chapter IV lays out all results from the analyses, and briefly describes the meanings of each result. Chapter V gives a more detailed explanation of the implications of these results, and recommendations for future work.

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II. DATA INTRODUCTION

A. CURRENT MILITARY POLICIES

Since the HIV epidemic began, "over 10,000 active duty military members have been diagnosed with HIV infection" (IDCRP 2015a). Each service in the U.S. military has its own guidelines regarding the treatment of HIV positive individuals, apart from the Marine Corps, which falls under Navy policy. While all policies recognize and reference the authority of national standards for HIV treatment, each service has different standards and levels of specificity for how to track engagement and clinical outcomes of their HIV positive patients. All policies condition the individual's retention in service on their ability to perform their duties, and access to necessary medical care.

All services acknowledge the precedence of national HIV treatment standards, as developed by the National Institutes of Health (NIH) and as such are nonspecific on treatment procedures or medication regimens. The NIH and World Health Organization (WHO) release guidelines for HIV care and updates them when new data or studies are available. Before 2009, the WHO recommended starting ART if a patient's CD4 count dropped below 200, or initiating when they came close to such a level, to prevent their CD4 counts going any lower (WHO 2006). Gradually, the treatment policies have become more inclusive, allowing patients with higher CD4 counts to begin treatment (WHO 2010, 2013, 2015). In fact, current NIH recommendations state that ART should be initiated immediately in all patients, regardless of age or CD4 count (NIH 2016).

Regarding specific medications, there are many regimens and specific drugs from which to choose, but there is a standardized regimen for those patients just beginning ART, known as "treatment-naïve" patients (NIH 2016). According to NIH, "more than 25 antiretroviral (ARV) drugs in 6 mechanistic classes are Food and Drug Administration (FDA)-approved for treatment of HIV infection." (NIH 2016). Among the classes of these drugs are nucleoside/nucleotide reverse transcriptase inhibitors (NTRIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitor (FI), integrase strand transfer inhibitor (INSTIs), and pharmacokinetic (PK)

enhancers, which are used to increase the effectiveness of other medications in the regimen. The current standard regimen for treatment-naïve patients is two NRTIs, plus an INSTI, NNRTI, or PK-enhanced PI. This regimen has been shown to increase CD4 counts in new patients (NIH 2016). The differences between these drugs, as well as their mechanisms and drug interactions, are beyond the scope of this thesis. For the purposes of this thesis, the drugs are assumed to have been administered correctly by the healthcare provider.

The U.S. Air Force details its guidelines for treatment in AFI 44–178 (SECAF 2014). The Air Force mandates, once an individual has tested positive for HIV, that the service member be counseled as soon as possible. A health evaluation is done upon the initial visit, as treatment is discussed and initiated. Six months after the initial visit, another evaluation is required to assess progress, after which, evaluations are mandatory every twelve months (SECAF 2014). The policy details that these visits are required, but not the only appointments which should be made, saying other clinical visits as part of the treatment regimen should be conducted as well. The policy also details that, should a service member show signs of psychiatric distress or deterioration as a result of the disease, they should receive the appropriate care. The policy mandates additional testing "as indicated to maintain compliance" (SECAF 2014).

The U.S. Navy is the most general in its guidelines regarding HIV treatment and engagement. The policy, Secretary of the Navy Instruction (SECNAVINST) 5300.30E, requires the frequency of evaluations to be determined by "health status" and "nationally accepted guidelines" (SECNAV 2012). The Navy also requires an evaluation of the individual's potential for transmission, mandating counseling for the patient's sexual partners, and evaluating any risks of exposure for other individuals the patient may have come into contact with (SECNAV 2012).

The U.S. Army has the most detailed guidance regarding care for HIV positive individuals. Army Regulation (AR) 600–110 mandates that after the initial positive test, the patient's commanding officer is immediately notified and required to counsel the patient face to face (Personnel General 2014). They are required to read a document detailing that individual's new obligations, risks, as well as restrictions, such as not

donating blood (Personnel General 2014). After the initial counseling, that individual is required to attend a psychiatric evaluation to determine their current state, and to provide a baseline in case of neurological deterioration due to the disease. After these initial evaluations, and in addition to all their regularly scheduled medical appointments for treatment, the soldier is required to receive a clinical evaluation twice yearly. Their commanding officer is notified of any noncompliance issues (Personnel General 2014).

B. COHORT INTRODUCTION

Combining all patients from each service, the NHS is a study under the IDCRP. The main goal of this work is to generate data and physical samples which can be referenced in many future studies. The program has several strategic aims which guide their research. This thesis, with its focus on engagement in care and on outcomes for active duty patients, focuses mainly on aims 1 and 2, as shown in Figure 1.

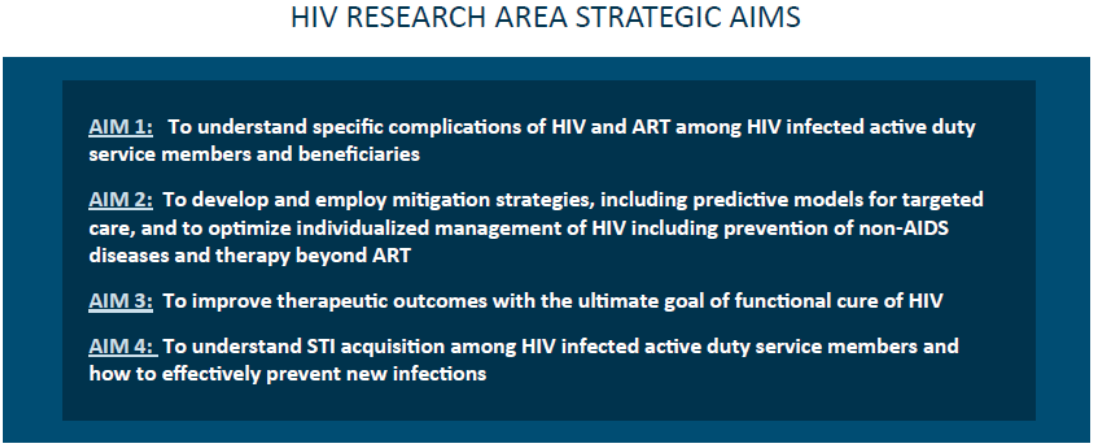

Figure 1. U.S. Military Natural History Study (NHS) Strategic Aims. Source: IDCRP (2015a).

The NHS has assembled a cohort of patients, whose demographic and clinical data, as well as tissue and serum samples, are collected and retained for future studies. Since 1986, over 6,000 active duty military members or their beneficiaries have participated in the NHS cohort. Currently, about 1,500 members of the cohort are still actively participating in data collection and sampling. This current cohort is racially

diverse, and nearly half were on active duty as of their last visit. Figure 2 shows the racial diversity of the patients who are currently active in this cohort.

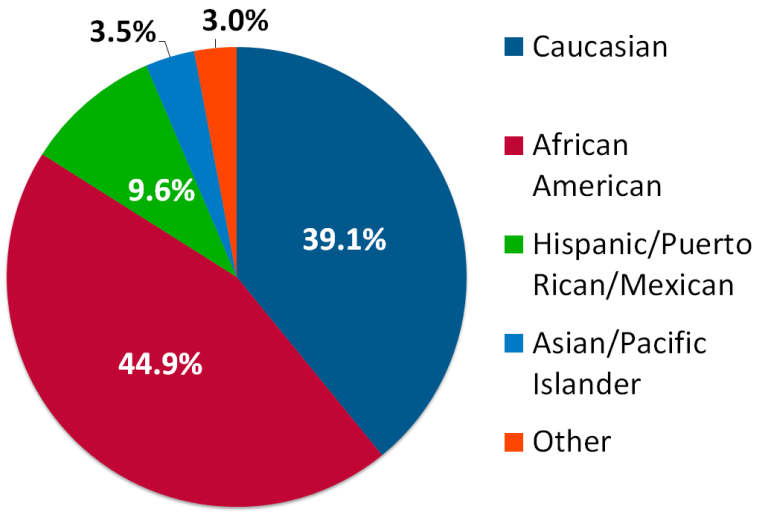

Figure 2. Racial Demographics of the Current NHS Cohort Study Source: IDCRP (2015b).

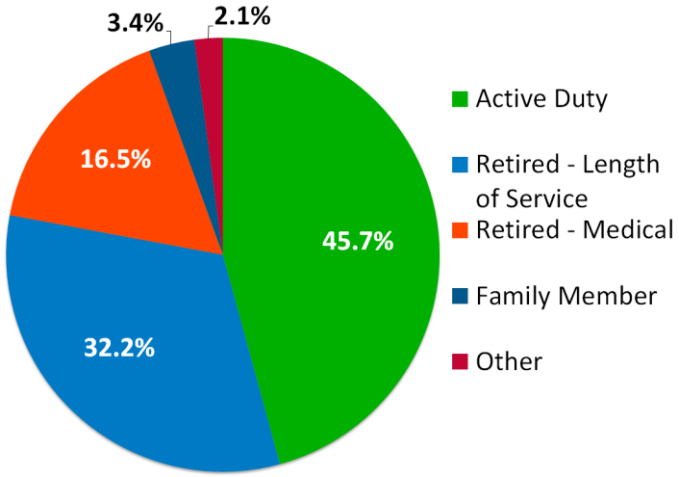

Figure 3. Career Status of the Current NHS Cohort. Source: IDCRP (2015b).

Figure 3 shows that the largest portion of the dataset comes from active duty members of the U.S. Military, with only a small number of the cohort being civilians, such as DOD service member beneficiaries. Currently, the NHS has three main research interests. First is the study of HIV outcomes, to include AIDS, cancer, neurocognitive

effects, and others. Another interest is on treatment outcomes, such as the outcome of ART, and any complications and costs associated with the treatment. Third is the epidemiology and prevention of HIV and other sexually transmitted infections (IDCRP 2015b).

To aid in these research interests, many types of data have been collected on the current cohort. Demographic data, to include age, gender, race, ethnicity, duty status, military specialty code, rank, marital status, and more, have been collected for each patient. Of particular interest to this research study is adherence data, which includes appointment test dates and pharmaceutical refill data (IDCRP 2015b). The dataset also includes medication regimen information as well, detailing which drugs the patients were treated with, and when (IDCRP 2015b). ART has been shown to be very effective when used correctly (UNAIDS 2014). As such, this study assumes correct implementation of ART. To judge the effectiveness of patient care, this study focuses on length of treatment and indicators of health, such as CD4 and viral load data. Also collected are clinical data, such as CD4 counts, CD8 counts (CD8 is a white blood cell similar to CD4), and viral load measures for each patient. The data are collected through in-person interviews, medical records, questionnaires, and automatic captures from online military health systems (IDCRP 2015b).

C. PRIOR ANALYSES

This dataset has been used to conduct other analyses. Marconi, et al. (2010) provided insights on the outcomes of ART combined with the effects of universal healthcare. In this study, the active duty cohort's viral load and clinical outcomes (AIDS, death, or none) were evaluated to determine how effective ART is when implemented in a population which has universal access to healthcare. The study showed that active duty rates of viral suppression and desirable outcomes were higher than other populations, and so it is likely that increased access to healthcare is an aiding factor in viral suppression.

Previous work on engagement in care in the military has been done by Mancuso (2016) with a subset of the data used in this thesis. Many of the concepts addressed in this thesis stem from this study. Mancuso (2016) provided some general descriptive statistics

of the study population, as well as data concerning the overall cascade of care data, and viral suppression timelines in his analysis. Some questions left unanswered by Mancuso (2016) were how HIV engagement differs by service, and what factors effect engagement.

D. STATISTICAL METHODS

Three main approaches were used to obtain the results of this study: descriptive analyses using unadjusted percentages, and survival function estimation using Kaplan-Meier estimates and Cox proportional hazards models.

1. Constructed Variables

To aid in the analysis, several variables were constructed or transformed from the given data. First, a discrete time variable was created, which ranged in value from 1 to 20, with each time representing a single 90-day increment from the date the patient was documented as HIV positive. This served to give all patients the same starting point in terms of known HIV status.

A variable named PCS was created, which indicated how many times the patient moved or made a Permanent Change of Station (PCS) while undergoing treatment. Each patient's PCS variable starts at 0, indicating this location is the first they have lived in since their diagnosis. When a patient makes a PCS, the PCS variable increments to 1, showing it is their first move since diagnosis, and so on. The PCS variable reaches values as high as 4 for some patients, indicating four moves since diagnosis.

To assess how a patient's ART treatment was implemented, several treatment-related variables were constructed. Time_TX, a variable, ranging from 1 to 20, indicates in which 90-day time period the patient began to receive ART. TX, a similar variable, is a binary with 0 signifying the patient is not being given ART, and a 1 indicating they have started to receive ART. Next, Met is a binary variable, which indicates if the patient's treatment at the time met (adapted) WHO HIV treatment initiation guidelines, or not. We acknowledge that the HIV treatment guidelines are a bit more nuanced than simply using

a CD4 indicator, to include AIDS-defining illnesses etc., WHO (2006, 2010, 2013, 2015). The adapted treatment initiation guidelines are laid out in Table 1:

Table 1. Treatment Guidelines for Starting ART in HIV+ Patients Adapted from World Health Organization (WHO) (2006, 2010, 2013, 2015).

Policy:	End Date:
CD4 < 200	Nov-09
CD4 < 350	Jan-13
CD4 < 500	Sep-15
Treat All Patients	Current

For the Met variable to be 1, indicating compliance with treatment guidelines, either the patient must have been treated with ART, or, if they were not, they must have exceeded the minimum CD4 count needed to begin treatment, as defined by the policies above. The variable TX_GROUP indicates which policy each patient began treatment under, ranging from 1, being the policy which was ended in November of 2009, to 4, being the current policy to treat all patients regardless of CD4 count. All patients in this cohort who began treatment fall into the first three categories, with no patient starting ART under the current policy.

Next, the age demographic variable was transformed into a factor with six levels, starting at under 20 then going up in five year increments until over 40. In addition, from CD4 measurements and time_TX, the variable BASE_CD4 was created, indicating the CD4 level of the patient at the time they started ART treatment. From the available adherence data in this cohort, calculated as the percent of doses of medication a patient took on time, the average adherence of each patient over the twenty quarter timeline was calculated. From this average adherence data, two binary variables were created: ADHERE_90 and ADHERE_95, which are zero if a patient's average adherence falls below the threshold (90% and 95%, respectively) and one if they meet or exceed the threshold.

Lastly, an outcome variable, or event of interest variable, was created: VS. This variable is a zero for each individual patient until the first time their viral load falls below 200, at which point it changes to 1 and remains 1 from there on. Viral suppression is a positive outcome, therefore patients who "survive" longer in the dataset and do not reach this state are considered to be in a worse health than those who reach viral suppression.

2. Unadjusted Percentages

To gain insight into the general trends throughout the data, mean values and percentages were computed. In the case of a missing value or null value, such observations were removed from the calculation. Racial and background demographic variables are recorded once per patient, while clinical variables can be recorded several times per patient, one for each encounter in which the variables were recorded. The clinical data were not normalized to provide an equal contribution per patient because patients with more clinical data are considered more informative to this study, and so have a larger influence on the initial descriptive statistics.

3. Kaplan-Meier Survival Analysis

For Kaplan-Meier estimates of the survival function, all patients are treated as if they entered at the same initial time (t = 0), and are removed from the number "at risk" (*n.risk*) as the event of focus occurs to them or if they are censored. The function S(t) is the probability that in individual "survives" to time t. It is estimated based upon how many individuals are at risk and how many of those individuals experience the event of interest up to time t. Specifically, let $0< t_1 < t_2 < \ldots < t_m$ be ordered observed "death" (or event) times, and let $n.risk_i$ and $n.event_i$ ($i = 1, \ldots m$) be, respectively, the number of individuals at risk, and the number of events to occur among those at risk at or before time t_i. Then, for right-censored data, the Kaplan-Meier estimator of S(t) is given by:

$$\hat{S}(t) = \begin{cases} 1 & \text{if } t < t_1 \\ \prod_{t_i \le t} \left[1 - \dfrac{n.event_i}{n.risk_i} \right] & \text{if } t \ge t_1 \end{cases}$$

The specific event used can be any binary event of interest to the researcher. In this study, the outcome of interest is viral suppression. Each patient receives a zero for

the outcome variable while they are still in the dataset, but as soon as they reach viral load below 200 cells per microliter, they are counted as a one, i.e. the event of viral suppression has occurred. As such, survival in the model is associated with a negative outcome – still being sick, while a "death" in the model actually represents a positive outcome for the patient.

This particular dataset includes what is known as "right-censoring", meaning data collection may stop (for reasons unrelated to the outcome event) before viral suppression is reached. In such cases, data for a particular patient is no longer available, so they are removed from the at risk group. This right-censoring is not counted as an event of interest, but does decrease the total remaining in the cohort, and as such means confidence intervals will widen with decreased cohort sizes as time progresses.

4. Cox Proportional Hazards Analysis

Cox proportional hazards models allow the survival function to be a function of covariates (see Diez 2013). Let $\boldsymbol{z}$ be a vector of covariates and let $\boldsymbol{\beta}$ be a corresponding vector of parameter coefficients. The conditional hazards function is $H(t \mid \boldsymbol{z}) = -\log S(t \mid \boldsymbol{z})$ where S(t|$\boldsymbol{z}$) is the survival function given covariates $\boldsymbol{z}$. The Cox proportional hazards model is a semi-parametric model where the hazards given covariates $\boldsymbol{z}$, is proportional to a baseline hazards, $H_0(t)$:

$$\mathrm{H}(t \mid \boldsymbol{z}) = H_0(t)\exp\{\boldsymbol{\beta}'\boldsymbol{z}\} \quad t > 0$$

Both $H_0(t)$ and $\boldsymbol{\beta}$ are estimated and, like the Kaplan-Meier estimator, those estimates can be based on right censored data. We note that this definition of the Cox proportional hazards model requires that the covariates be time independent (e.g., sex, service, etc.) However, the Cox proportional hazards model can be extended to include certain time varying covariates (e.g., rank, age, etc.)

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III. DATA AND METHODOLOGY

A. DATA DESCRIPTION

This thesis uses data from a cohort made up of HIV-infected military service members. Every individual has all demographic, clinical, and encounter data points stored along with a de-identified variable called "MUCKED_PIN," by which they are identified for the remainder of their participation in the cohort.

The data were processed by the primary investigators at the NIH in Bethesda, MD, to ensure the sample was complete, and de-identified. The processed dataset has 904 cohort participants. The data were contained in 11 comma-separated value spreadsheets. Each spreadsheet contains a different aspect of the dataset. One contains all CD4 counts and dates from patient tests, and two contain demographic information. The first demographic spreadsheet contains data regarding gender, rank, first diagnosis, first and last visits, death, etc. The second contains data related to the mode of transmission. Another two spreadsheets contain doctor-patient encounter data, including the date of each appointment, the doctor's diagnosis, represented by an ICD9 code, as well as the method by which the patient received medication. Two spreadsheets contain information related to the ART each patient is undergoing. They detail which medications the patient is taking, in what quantities, the medicinal class of the prescriptions, and binary variables indicating presence or absence of each of the main types of prescription regimens. One spreadsheet contains adherence data, describing the visit date by the patient, and the percent adherence to the medication regimen. Two more sheets give PCS data for each patient, describing if they PCS'ed during treatment, and how many times. Lastly, there is also a spreadsheet with the viral load results of each patient's tests, containing multiple entries per patient, one for each test conducted. There are also two definition spreadsheets which describe the abbreviations and codes used for each of the variables.

B. DATA ELEMENT DESCRIPTIONS

The original dataset contains 133 variables, though the variables of most interest as they pertain to our research questions are variables detailing relative health, such as

CD4, CD8, and viral load, and variables detailing engagement such as adherence data and appointment information. Also of interest are demographic data such as race, rank, and gender.

1. Maximum CD4, CD8, and Viral Load Count by Time

For every test a patient submits, CD4 counts are recorded. Dates of the tests vary widely, sometimes with several tests over a couple of months, and sometimes with no tests for several months at a time. As such, a standardized time unit was created, with a division every 90 days. The zero date for each patient is the date of their first positive diagnosis (day zero). When tests are conducted, they fall within 90-day divisions of separation from day zero. For each patient, the maximum value of their CD4 count was taken for each 90-day increment, for 20 such increments, which provides roughly 5 years-worth of time steps for analysis. If a patient does not have data for one of the time steps, the result is assigned an NA value, where NA indicates a missing value. As such, a dataset was created which contained maximum CD4 values for time steps (i.e., 90-day windows) 1 through 20 for every patient. The same methods were applied to create similar variables for CD8 count and viral load.

2. Background Demographics

Each patient was labeled with one of 6 categories of racial background: White, African American, Native Hawaiian or Pacific Islander, Asian, American Indian or Alaska Native, or other. A binary variable indicates male or female. Marital status data were available, having the following levels: not married, married – living together, married – not living together, married – living apart – not separated, married – separated, widowed, divorced, and not married – living together (cohabitative).

3. Military Demographics

Military specific data were collected on each patient. Each patient's rank at diagnosis is recorded as officer, warrant officer, enlisted, N/A (where N/A denotes "not applicable"), or missing. No further resolution, such as individual enlisted or officer ranks, is given, so it is impossible to tell the exact rank of the patients. Each patient's

service affiliation is also recorded as Army, Navy, Air Force, Marines, or Coast Guard. While Coast Guard is included as a possible level for the variable, no Coast Guard patients exist in this dataset. Each patient's duty status at diagnosis was also available; however, the variable is largely irrelevant, as all 904 members of the cohort were on active duty at the time of diagnosis.

4. Risk Factor Variables

Risk behaviors based upon patient surveys were also available. Risk of alcohol abuse was a trinary variable: no use, not at risk, or at risk. Smoking was a binary variable: yes or no. Other risk factors included the possible method of transmission, which is based upon patient surveys regarding activities they admit to engaging in which carry with them high-risk for HIV transmission. The levels of the mode of transmission variable include unknown, same sex intercourse, opposite sex intercourse, blood products, injection drugs, or other. It should be noted that mode of transmission data can contain multiple responses for each patient, as it does not identify for certain how the patient was infected, but identifies the risk behaviors which the patient reports engaging in which could have led to infection.

5. Clinical Variables

Each patient has a year of positive diagnosis listed, along with their date of diagnosis. Each patient also has an estimated year and date of seroconversion (seroconversion is the time at which HIV reaches high enough levels in the body to be detectable in a HIV test). Other variables include the number of drugs each patient was on during treatment, as well as the class of each drug, and the specific name and type of the drug. Another variable available for each patient is adherence data, usually calculated by the medical provider, who counts how many medication doses the patient missed over the course of their prescription.

C. DESCRIPTIVE STATISTICS

Based upon the variables described above, general trends in the data can be summarized. The make-up of the cohort can be compared with the rest of the military

population. There are several key similarities and differences, which are highlighted below. The clinical outcomes are also summarized below, giving a general idea of the overall health and effectiveness of care in the study population.

1. Cohort Profile

To determine the demographic profile of the cohort and how it compared to the rest of the military, the background demographics were analyzed for similarities and differences, starting with racial background shown in Figure 4.

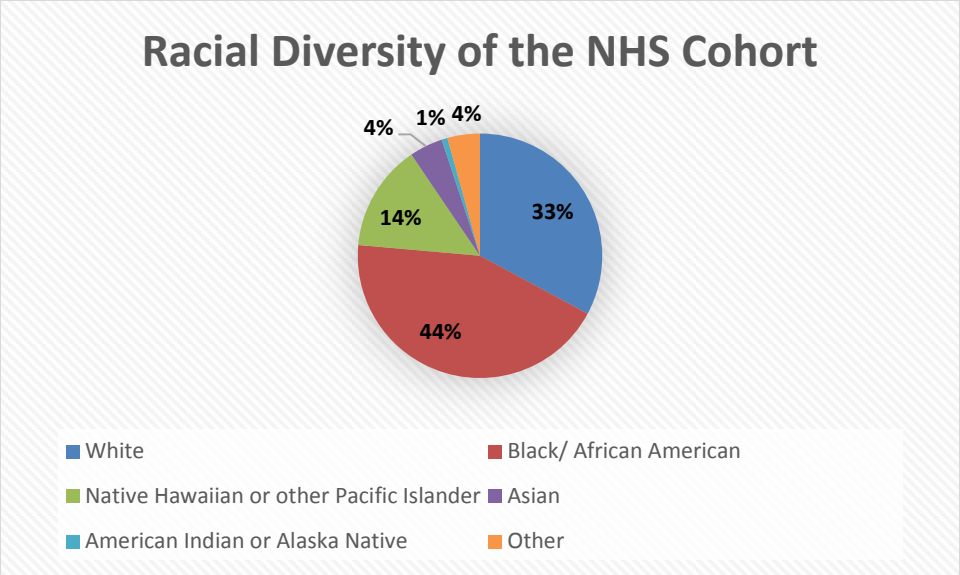

Figure 4. Racial Profile of the Study Cohort

While Figure 2 covers the entirety of the IDCRP working group, from 1996 to the present, Figure 4 only considers those patients who are included in the subset of the cohort, which is used for this analysis. From these basic statistics, it is evident there is a disparity between the study cohort and the rest of the military. The majority of the U.S. military (70.7%) is White (DOD 2015), while in this dataset, the inverse is true, with Whites making up only 33% of the total cohort. The largest population in the study is African Americans, at 44%, whereas they only make up about 17% of the total military force (DOD 2015). Asian service members make up 4% in both the total force and this study cohort, and American Indians or Alaska Natives are about 1% in both populations

as well. Native Hawaiians and Pacific Islanders only make up about .9% of the total force, while in this study, they make up a disparate 14% of the study cases.

Regarding gender, there is a disproportionate number of male members of this cohort to females—97% of the cohort is male, with 3% female. In the rest of the military, 84.5% are male and 15.5% are female (DOD 2015).

Statistics for the total military force only have variables for never married, married, or divorced, as such, the statistics of this cohort were combined to make a comparison. Firstly, 65.2% of the study cohort is single, 28.1% is married, and 3.4% is divorced, versus the total military force which is 54.3% married, 41.6% never married, and 4.0% divorced. There is a much higher percentage of single members of the cohort than in the military at large (DOD 2015).

2. Military Profile

Regarding military-specific statistics, the officer-enlisted ratio is similar to the total military force. The cohort contains 11% officers and 88% enlisted, while the military at large contains 17.7% officers and 82.3% enlisted (DOD 2015).

However, this similarity ends when viewing the service branch. While the regular military is composed of about 37.4% Army, 24.8% Navy, 14.1% Marine Corps, and 23.6% Air Force (DOD 2015), the cohort is composed of almost half Navy, 20% Army and Air Force, and only about 10% Marine Corps, as shown in Figure 5.

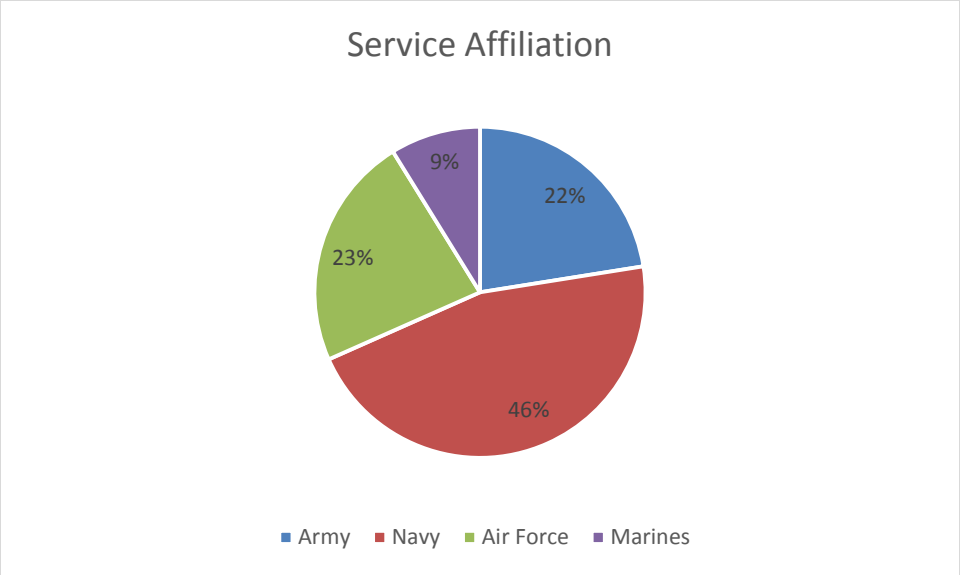

Figure 5. Service Affiliation of the Study Cohort

It should be noted how disproportionately represented the Navy is in the HIV positive cohort, accounting for almost half of the study population, while the regular Navy only accounts for about one fourth of the total military.

3. Clinical Profile

According to the CDC, in 2011, 24% of active duty military members reported smoking, versus 27.1% in this study cohort (CDC 2017). A 2008 study found that "20% of military personnel reported binge drinking every week in the past month" (NIH 2013). While metrics change over time, in this study cohort, 27% of participants were considered at risk for alcohol abuse, 67.5% reported using alcohol, but were not considered at risk, and 22.5% reported no alcohol use.

Continuing with risk behaviors, the majority of participants (64.8%) were of "unknown" mode of transmission. This could be because of missing data, or because patients declined to respond. As noted before, this metric allows for multiple responses from each patient, and assesses risk activities associated with HIV infection, so actual mode of transmission cannot be known for each patient. However, of those who responded in the cohort, 24.6% listed same sex intercourse as a possible mode of transmission, 8.3% listed opposite sex, 0.4% listed blood products, and 1.6% listed

"other." Only 0.2% of the cohort listed injection drug use as a possible mode of transmission, which is to be expected, considering the military's zero tolerance policy on illicit drug use.

Each patient's adherence data contain multiple doctor visits in which percent adherence is measured. These data contained 5056 individual observations for the 907 patients in the cohort. The data were not separated or averaged by individual, as total adherence per visit was of interest, rather than average adherence by patient. The data were divided into several increments, and total counts were calculated for each increment, as shown in Figure 6.

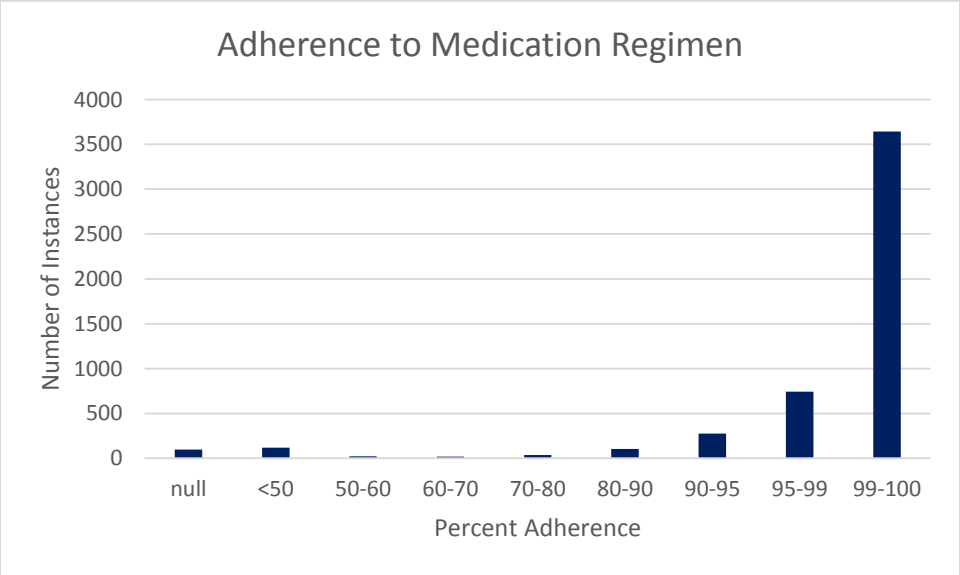

Figure 6. Adherence Data of the Study Cohort

Seventy-two percent of the responses indicated 99% or greater adherence to the regimen, 92.2% of the responses indicated 90% or greater adherence, meaning only 7.8% of the responses were less adherent.

4. CD4, Viral load, and Viral Suppression

90-90-90 specifies that out of the population, 90% should know their status, of that 90%, another 90% should be consistently engaged in ART, and of that percent, 90%

should reach viral suppression. As such, closer analysis of the study population, to separate adherent and non-adherent patients, would aid in analysis of how close to reaching the target the U.S. military truly is. However, to get a general view of how patient health changes over time, in this section we study changes in CD4 levels, viral load, and viral suppression over time, excluding missing values. Time zero for each patient was considered to be their documented positive date, as such, the date of time zero is different for every patient, but clinically speaking, each patient should be in relatively the same state at such a time because of the regular HIV tests service members need to receive. We note that each patient's record contains an estimated seroconversion date (i.e. the earliest date that HIV antibodies could be detected). As shown in Figure 7, HIV positive results rarely come later than one year after seroconversion.

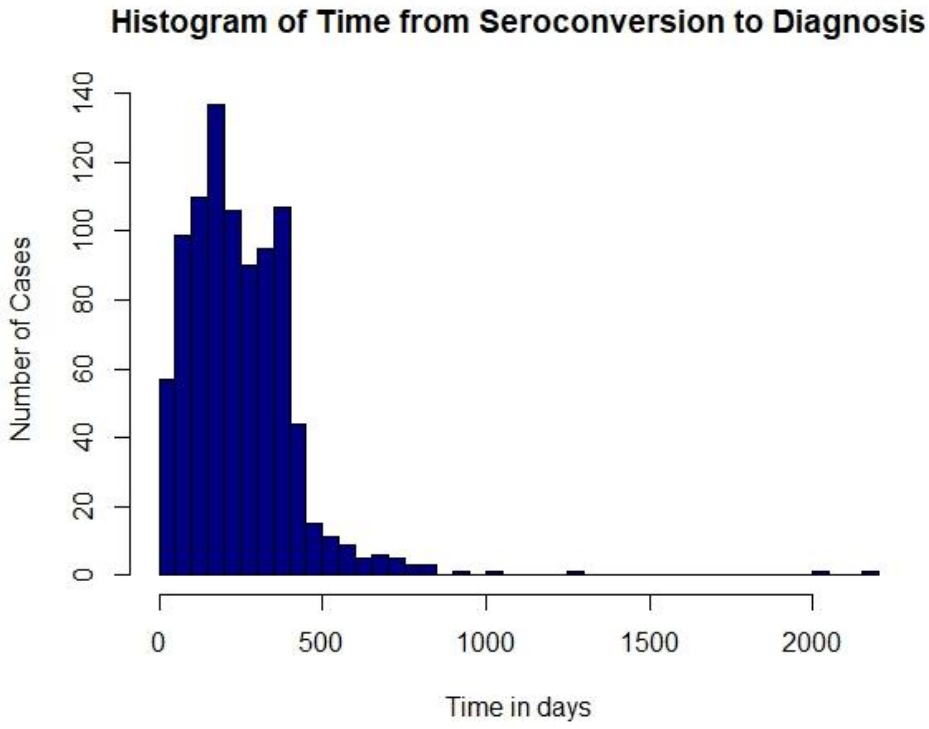

Figure 7. Time from HIV Seroconversion to Diagnosis

The average time from estimated seroconversion to documented positive dates is 249 days, though there are some extreme outliers well beyond the 1, 2, and even 3 year marks. However, without patient-specific data, it is impossible to exactly determine the reason for such long intervals. It should be noted that the majority of patients contained in the dataset were identified quickly.

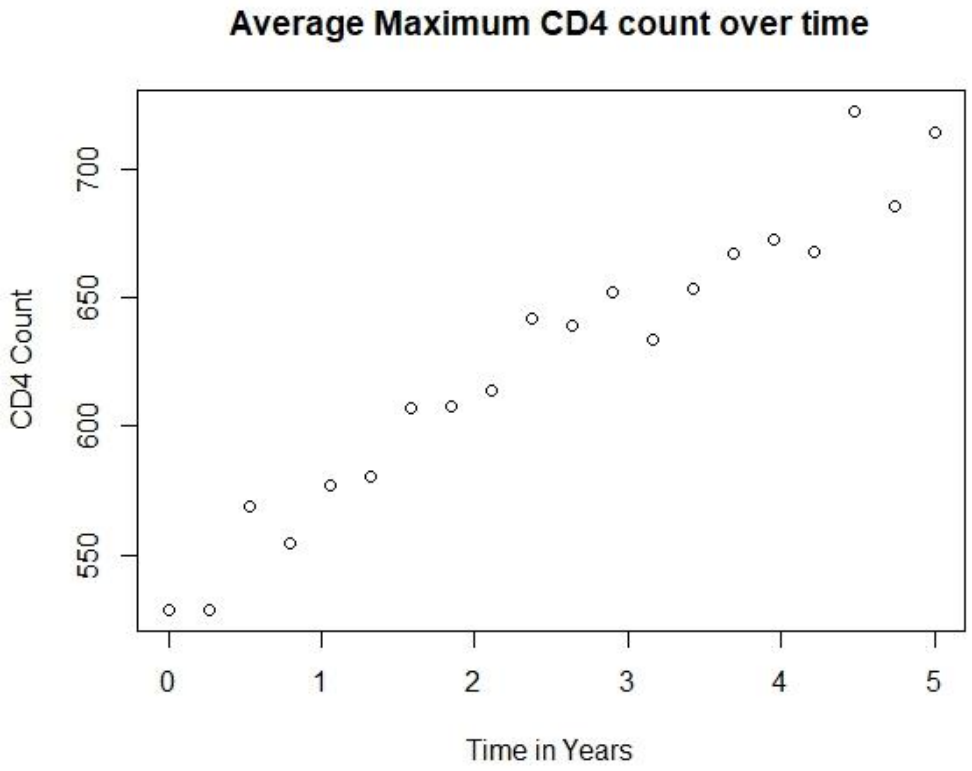

Figure 8. Average Maximum CD4 Count over Time in the Continuum of Care

In Figure 8, we plot the average value of all patients' maximum CD4 value over time (excluding patients with missing values). As the patients pass through the continuum of care, average maximum CD4 counts tend to increase, indicating a healthier immune system. While this graph looks like compelling evidence for effectiveness of treatment, more treatment data are needed before more robust conclusions can be drawn. However, on a preliminary basis, these data appear to indicate effective treatment and increased patient health along the continuum of care.

Viral load data were handled much like CD4 data, with one important difference in interpretation. While maximum CD4 values provide a best-case estimate of patient health, maximum viral load values provide a worst-case estimate of patient health. However, as can be seen from Figure 9, both tell the same story of improved patient health with increased time in system. Before a patient begins treatment, there is very little to restrict the virus from multiplying, as such, at time zero, viral load is extremely high, and decreases dramatically once treatment starts, and continues to decrease, indicating a trend in improved patient health over time.

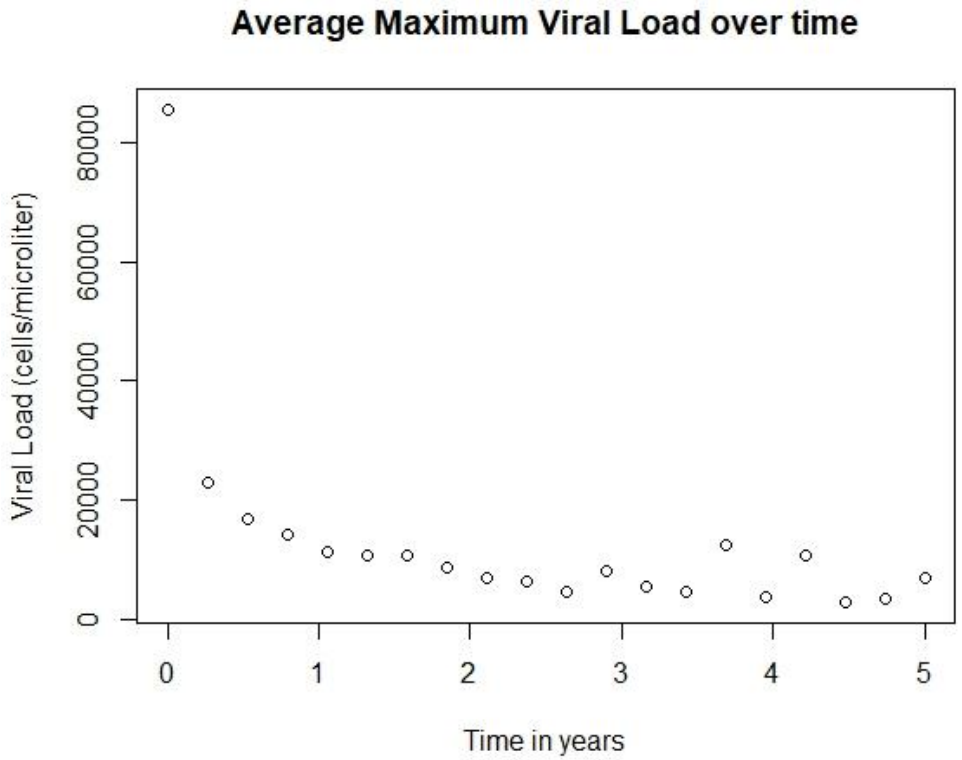

Figure 9. Viral Load over Time

Since viral load seems to be decreasing, the data were inspected to see what percentage of patients reached viral suppression within the given time frame. Enough patients did reach suppression to warrant a descriptive graph of the trend, shown in Figure 10: At time zero, no patients are in viral suppression; however, as treatment progresses, the percentage who are in viral suppression increases.

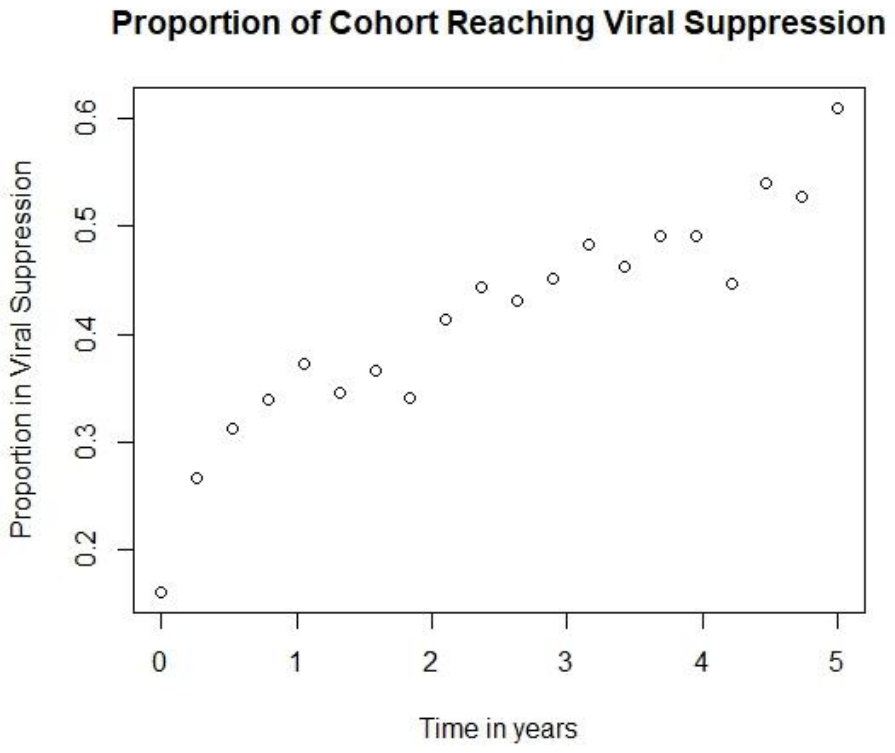

Figure 10. Proportion of Viral Suppression in the Cohort over Time

The data used in Figure 10 includes patients who were treated and untreated. To gain a more accurate estimate of the proportion of the cohort who are suppressed in a given time frame, only patients who were not missing for that time frame were included, as a preliminary method to account for lack of data as time progresses. For this analysis, the common threshold of viral load less than 200 counts per microliter was used to indicate suppression.

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IV. RESULTS AND ANALYSIS

A. EXPLORATORY SURVIVAL ANALYSIS

Survival analyses using Kaplan-Meier and Cox proportional hazards estimates of the survival functions were performed from the "survival" package (Therneau 2015) in R (R Core Team 2016). An object of class "Surv" was created using the "Surv" function. The time index used was the "time" variable in the dataset, and the outcome variable was the "VS" binary variable from the dataset. VS =1 indicates the person going into viral suppression, otherwise, VS = 0. Therefore, longer "survival" in the at risk group is a negative outcome, while attaining viral suppression and dropping from the at risk group is a desirable outcome. In this survival analysis, the data can be right censored. Of the 904 patients in the analysis, 789 achieved viral suppression by time t = 20 (1800 days). Of the other 115 patients who never reached viral suppression, 37 of them remained in the at risk group at time t = 20. As such, 78 out of the 904 patients are right-censored without a known reason. Because patients are not removed from the at risk group for health or treatment reasons, we assume right censoring is independent of viral suppression times. One major assumption of the analysis was that, if a patient's viral suppression status was not known for a given time period (but the patient was known to still be part of the study cohort i.e. had data for later time periods), VS was set to zero. As such, a patient could possibly have reached viral suppression in an earlier time period in which data was not available, but they are not counted as such until the event is known. Thus, all estimated survival functions for the time until viral suppression give a conservative upper bound. In this section, we look at differences in survival functions for each variable, one at a time. While separation by one variable at a time cannot give a complete picture of interactions between the factors available in the data, it serves as an exploratory analysis to identify potentially important variables and begin to understand how each factor effects survival.

1. Survival Functions by Treatment

We first estimate the survival function as a function of the variable "TX" for treatment. Of all patients in the dataset, 828 were treated, and 76 were never treated. Also

of note in this section is how patients move between the two groups. A patient may be untreated for some time periods, and begin treatment later, at which point he or she moves to the at risk group in the treated cohort. As such, the number at risk in the treated cohort may increase as time progresses. However, never will a patient move from treated to untreated. For the plotted estimated survival functions with time-dependent variables, individuals are assumed to remain in the cohort in which they started, rather than moving between groups as they do in the survival function estimate tables.

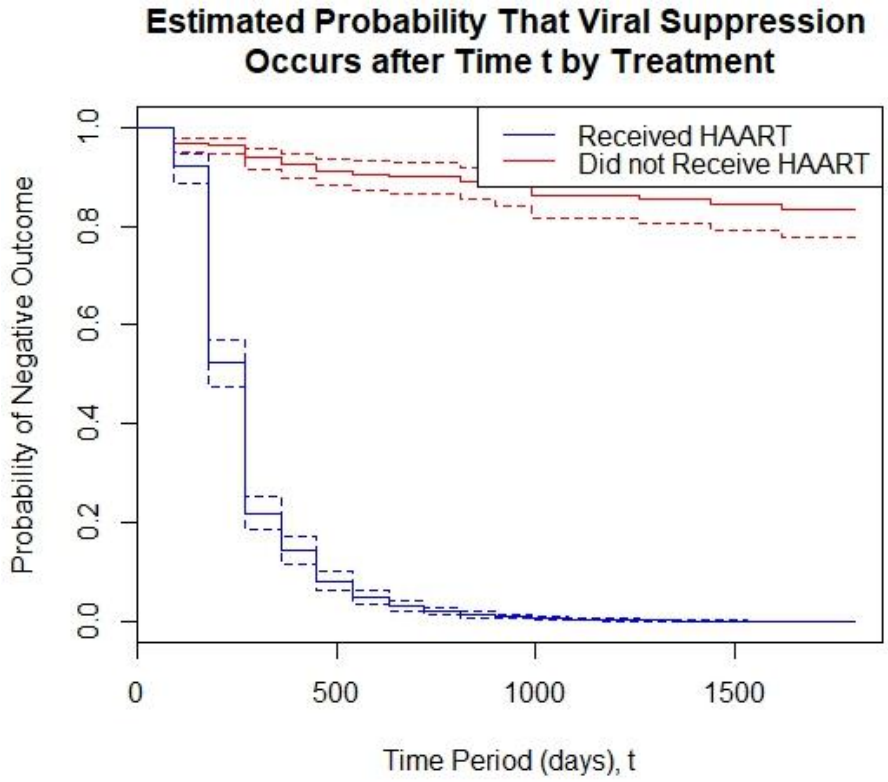


Figure 11. Estimated Survival Function of Viral Suppression Times by Treatment with 95% Confidence Intervals (Dotted Lines)

The estimated survival functions for viral suppression time by treatment plotted in Figure 11 display the expected results: those who are treated for their disease have a higher chance of attaining a desirable outcome early—viral suppression—while those who go untreated remain at much higher risk for negative outcomes.

Table 2. Estimated Survival Function of Treated Individuals

Treated			
t	n.risk	n.event	$\hat{S}(t)$
90	328	26	0.921 (0.886 , 0.945)
180	420	181	0.524 (0.476 , 0.569)
270	301	175	0.219 (0.185 , 0.255)
360	162	56	0.144 (0.117 , 0.173)
450	152	64	0.083 (0.065 , 0.104)
540	117	47	0.050 (0.037 , 0.065)
630	97	35	0.032 (0.023 , 0.043)
720	86	28	0.021 (0.015 , 0.03)
810	73	25	0.014 (0.009 , 0.02)
900	61	18	0.010 (0.006 , 0.015)
990	55	14	0.007 (0.005 , 0.011)
1080	54	17	0.005 (0.003 , 0.008)
1170	56	14	0.004 (0.002 , 0.006)
1260	49	14	0.003 (0.002 , 0.005)
1350	42	12	0.002 (0.001 , 0.003)
1440	38	9	0.001 (0.001 , 0.003)
1530	37	9	0.001 (0.001 , 0.002)
1620	31	4	0.001 (0.001 , 0.002)
1710	35	5	0.001 (0 , 0.002)
1800	31	6	0.001 (0 , 0.001)

Table 2 shows the estimated survival function by time period for all treated individuals in the cohort. The time dependency of this variable is readily apparent, as the number treated at risk increases from time t = 1 (90 days) and t = 2 (180 days). The chance that a treated individual remains non-virally suppressed decreases quickly, until survival nearly reaches zero by the end of the period of observation.

Table 3. Estimated Survival Function of Untreated Individuals

Untreated			
t	n.risk	n.event	$\hat{S}(t)$
90	576	19	0.967 (0.949 , 0.979)
180	439	1	0.965 (0.946 , 0.977)
270	383	10	0.940 (0.914 , 0.958)
360	335	5	0.926 (0.897 , 0.946)
450	283	4	0.913 (0.881 , 0.936)
540	249	2	0.905 (0.872 , 0.93)
630	219	1	0.901 (0.867 , 0.927)
810	181	2	0.891 (0.854 , 0.919)
900	164	2	0.880 (0.84 , 0.911)
990	149	3	0.863 (0.817 , 0.898)
1260	107	1	0.854 (0.806 , 0.892)
1440	91	1	0.845 (0.793 , 0.885)
1620	79	1	0.834 (0.777 , 0.878)

Table 3 shows the estimated survival function by time period for individuals who are not given ART. The untreated cohort fares significantly worse than the treated one. Survival in the at-risk population is almost the inverse of the treated population. About

80% of those who are never treated are estimated to remain non-virally suppressed by the end of the observed period. Note how quickly the number at risk diminishes, due to patients moving to the treated cohort, but how few events of viral suppression occur for the untreated individuals, leaving their survival relatively high by t = 20 (1800 days).

2. Survival Rates by Treatment Group

Next, the cohort of patients was partitioned into the three treatment policies mentioned earlier, CD4 < 200, CD4 < 350, and CD4 < 500. The Kaplan-Meier survival curves estimated for each treatment group show differences between the distributions of patient viral suppression times, given that a patient is assigned to exactly one treatment group. The treatment group is time-independent, as it is only affected by when the patient entered the cohort, and not on what happens to them as they move through their cascade of care. As such, the number at risk will never increase.

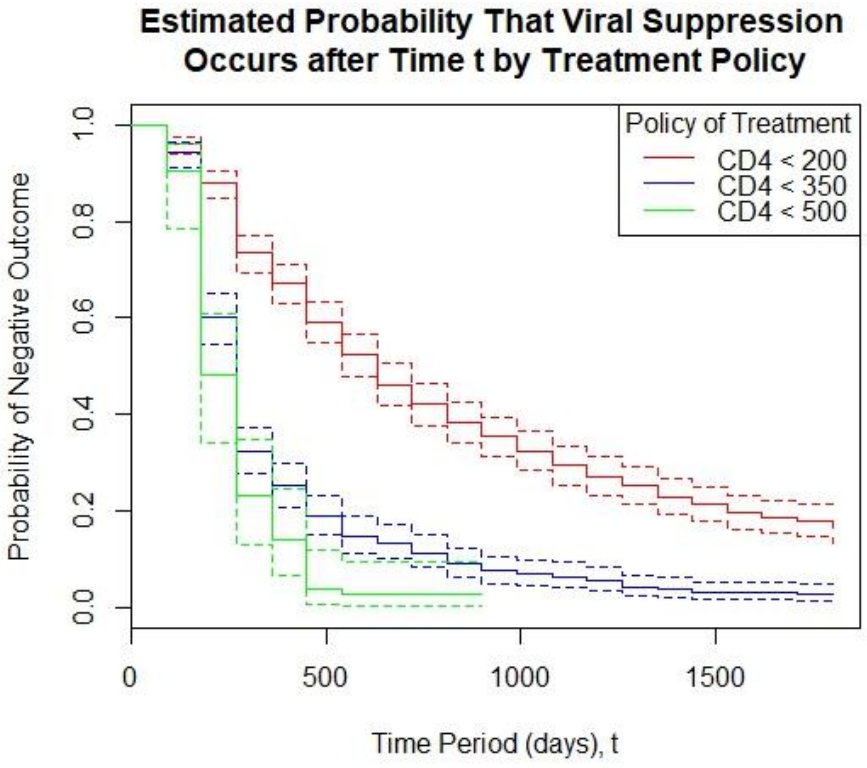


Figure 12. Estimated Survival Function of Viral Suppression Times by Treatment Policy with 95% Confidence Intervals (Dotted Lines)

Much like the division by treatment, the results of the survival analysis depicted in Figure 12 are expected. More inclusive treatment policies (allowing healthier individuals to start treatment earlier) increase the probability of reaching viral suppression sooner. The following survival tables do not take into account patient's actual starting CD4 values, which are analyzed later, but merely the policy they were diagnosed under.

Table 4. Estimated Survival Function for Treatment Group 1

Treat if CD4 < 200			
t	n.risk	n.event	$\hat{S}(t)$
90	504	20	0.96 (0.939 , 0.974)
180	484	41	0.879 (0.847 , 0.905)
270	443	73	0.734 (0.693 , 0.77)
360	371	31	0.673 (0.63 , 0.712)
450	339	41	0.591 (0.547 , 0.633)
540	298	34	0.524 (0.479 , 0.566)
630	264	31	0.462 (0.418 , 0.505)
720	235	21	0.421 (0.378 , 0.464)
810	214	19	0.384 (0.341 , 0.426)
900	193	15	0.354 (0.312 , 0.396)
990	178	15	0.324 (0.284 , 0.365)
1080	163	15	0.294 (0.255 , 0.334)
1170	148	11	0.272 (0.234 , 0.312)
1260	137	10	0.252 (0.215 , 0.291)
1350	127	11	0.231 (0.195 , 0.268)
1440	116	8	0.215

Treat if CD4 < 200			
t	n.risk	n.event	$\hat{S}(t)$
			(0.18 , 0.252)
1530	108	9	0.197 (0.163 , 0.233)
1620	99	5	0.187 (0.154 , 0.222)
1710	94	4	0.179 (0.147 , 0.214)
1800	90	6	0.167 (0.136 , 0.201)

Table 4 addresses the most restrictive treatment policy. Here, a 90% chance of viral suppression is not reached within the given time frame.

Table 5. Estimated Survival Function for Treatment Group 2

Treat if CD4 < 350			
t	n.risk	n.event	$\hat{S}(t)$
90	348	20	0.943 (0.912 , 0.963)
180	328	119	0.601 (0.547 , 0.65)
270	214	98	0.326 (0.277 , 0.375)
360	113	25	0.254 (0.209 , 0.3)
450	89	22	0.191 (0.152 , 0.234)
540	65	14	0.15 (0.115 , 0.189)
630	51	5	0.135 (0.102 , 0.173)
720	46	7	0.115 (0.084 , 0.151)
810	39	8	0.091 (0.064 , 0.124)
900	31	5	0.076 (0.051 , 0.108)
990	26	2	0.071 (0.047 , 0.101)
1080	24	2	0.065 (0.042 , 0.094)

Treat if CD4 < 350			
t	n.risk	n.event	$\hat{S}(t)$
1170	22	3	0.056 (0.035 , 0.084)
1260	19	5	0.041 (0.024 , 0.066)
1350	14	1	0.038 (0.021 , 0.062)
1440	13	2	0.032 (0.017 , 0.055)
1710	11	1	0.029 (0.015 , 0.051)

Table 5 shows the estimated survival function of the second treatment group, with a policy which was medium-restrictive, performed much better than the first treatment group, reaching about 97% chance of viral suppression by t = 20. The confidence intervals of both curves do not overlap, showing how different their survival functions are.

Table 6. Estimated Survival Function for Treatment Group 3

Treat if CD4 < 500			
t	n.risk	n.event	$\hat{S}(t)$
90	52	5	0.904
180	47	22	0.481 (0.341 , 0.608)
270	27	14	0.232 (0.131 , 0.349)
360	13	5	0.143 (0.066 , 0.247)
450	7	5	0.041 (0.008 , 0.122)
540	3	1	0.027 (0.004 , 0.096)

Table 6 shows the estimated survival function by quarter of the least restrictive treatment policy patients. Sample size becomes an issue in this at risk group, as this is the most recent policy, with the least amount of accumulated data. This policy, like the

second most restrictive policy, reaches about 97% chance of viral suppression by the end of the observed periods. However, they reach it much sooner than the medium restrictive policy, achieving this low survival function estimate by time t = 6 (540 days).

3. Survival Analysis by Baseline CD4

Next, the cohort of patients who were treated was partitioned into the different levels of CD4 when treatment began. This grouping variable differs from the treatment group variable in that this variable is taken from each patient's actual baseline CD4 level at the start of treatment, regardless of the time or policies in effect when treatment was begun. This too is a constant variable, with no time dependency. It is only the patient's initial CD4 measure upon start of ART.

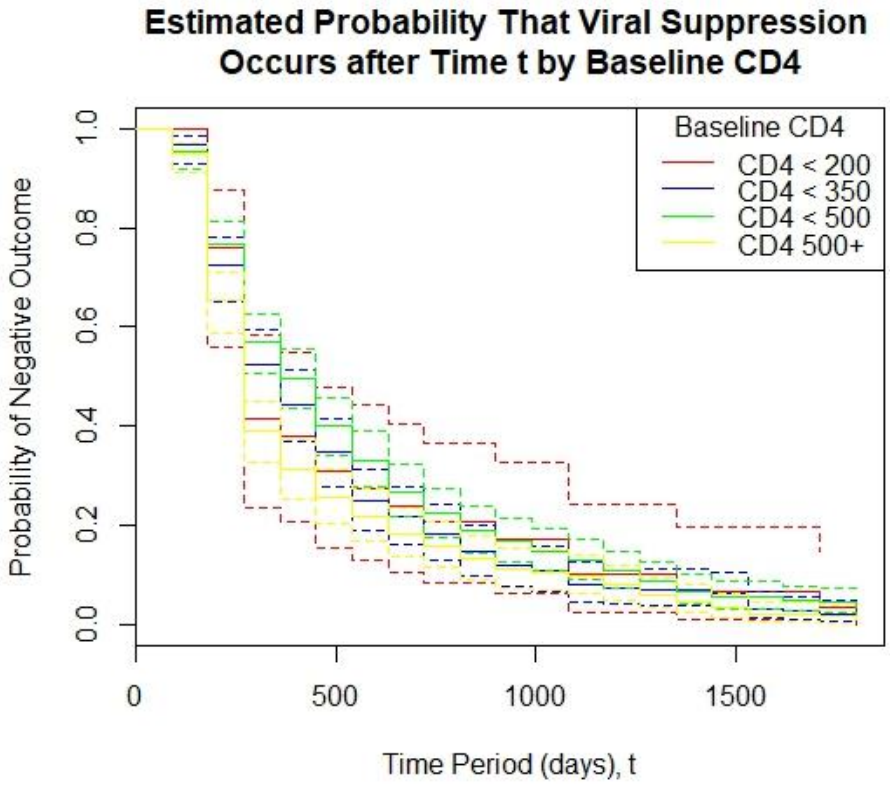


Figure 13. Estimated Survival Function of Viral Suppression Times by Baseline CD4 at Treatment Initiation with 95% Confidence Intervals (Dotted Lines)

This estimated survival functions in Figure 13 reinforce the point made in the earlier analysis by treatment group. Those who start treatment as healthier individuals will reach viral suppression faster than those who are already less healthy when they begin treatment. However, confidence intervals do overlap often, so a closer look at the data is necessary.

Table 7. Estimated Survival Function if Baseline CD4 <200

Base CD4 < 200			
t	n.risk	n.event	$\hat{S}(t)$
180	29	7	0.759 (0.559 , 0.877)
270	22	10	0.414 (0.237 , 0.583)
360	12	1	0.379 (0.209 , 0.549)
450	11	2	0.31 (0.156 , 0.479)
540	9	1	0.276 (0.131 , 0.443)
630	8	1	0.241 (0.107 , 0.405)
720	7	1	0.207 (0.084 , 0.367)
900	6	1	0.172 (0.063 , 0.327)
1080	5	2	0.103 (0.026 , 0.243)
1350	3	1	0.069 (0.012 , 0.198)
1710	2	1	0.035 (0.003 , 0.149)
1800	1	1	0 (NA , NA)

In Table 7, patients who started treatment with a baseline CD4 under 200 showed strong estimated survival functions throughout the observed time frame. Sample size causes issues in this table, as lack of events in certain periods such as t = 9 (810 days) causes those periods to be removed from the table. This happens if nobody reaches viral suppression in a

given time period, so there is no change in the survival function for that time. These individuals reach 0% estimated chance of survival by the end of the observed time.

Table 8. Estimated Survival Function if Baseline CD4 200-350

Base CD4 200-350			
t	n.risk	n.event	$\hat{S}(t)$
90	184	6	0.967 (0.929 , 0.985)
180	178	45	0.723 (0.652 , 0.782)
270	135	37	0.525 (0.45 , 0.594)
360	97	15	0.444 (0.371 , 0.513)
450	83	18	0.347 (0.28 , 0.416)
540	64	18	0.25 (0.19 , 0.314)
630	46	6	0.217 (0.161 , 0.279)
720	40	6	0.185 (0.132 , 0.244)
810	34	7	0.147 (0.1 , 0.202)
900	27	5	0.119 (0.078 , 0.171)
990	22	2	0.109 (0.069 , 0.158)
1080	20	5	0.081 (0.048 , 0.127)
1170	15	1	0.076 (0.044 , 0.12)
1260	14	1	0.071 (0.04 , 0.114)
1440	13	1	0.065 (0.036 , 0.107)
1530	12	6	0.033 (0.013 , 0.066)
1620	6	1	0.027 (0.01 , 0.059)
1710	5	1	0.022 (0.007 , 0.051)

As seen in Figure 13 and Table 8, with the increase in baseline CD4, not much changes. The estimated survival function is very similar to the first level, however, sample size is slightly larger, and so confidence bounds are tighter. Small sample size again shows lack of events at certain intervals, leaving out those time periods in the table. In the end, the estimated survival function was very similar to that of the first group in Figure 13.

Table 9. Estimated Survival Function if Baseline CD4 350-500

Base CD4 350-500			
t	n.risk	n.event	$\hat{S}(t)$
90	269	13	0.952 (0.918 , 0.972)
180	256	50	0.766 (0.711 , 0.812)
270	207	53	0.57 (0.508 , 0.626)
360	155	20	0.496 (0.435 , 0.554)
450	134	26	0.4 (0.341 , 0.458)
540	107	18	0.333 (0.277 , 0.389)
630	89	17	0.269 (0.218 , 0.323)
720	72	12	0.224 (0.177 , 0.276)
810	60	9	0.191 (0.146 , 0.24)
900	51	6	0.168 (0.126 , 0.215)
990	45	5	0.15 (0.11 , 0.195)
1080	40	5	0.131 (0.094 , 0.174)
1170	35	6	0.108 (0.075 , 0.149)
1260	29	5	0.09 (0.059 , 0.128)
1350	24	6	0.067 (0.041 , 0.102)
1440	18	3	0.056 (0.033 , 0.088)

Base CD4 350-500			
t	n.risk	n.event	$\hat{S}(t)$
1620	15	2	0.049 (0.027 , 0.079)
1710	13	1	0.045 (0.025 , 0.074)
1800	12	2	0.037 (0.019 , 0.065)

Table 9 shows how the estimated survival function decreases somewhat as CD4 increases, indicating healthier patients The estimated survival function shows very similar results compared to the first two functions.

Table 10. Estimated Survival Function if CD4 >500

Base CD4 500+			
t	n.risk	n.event	$\hat{S}(t)$
90	236	12	0.949 (0.912 , 0.971)
180	224	70	0.653 (0.588 , 0.71)
270	156	63	0.389 (0.327 , 0.45)
360	92	18	0.313 (0.255 , 0.372)
450	73	13	0.257 (0.203 , 0.314)
540	60	9	0.219 (0.168 , 0.273)
630	51	8	0.184 (0.138 , 0.236)
720	44	6	0.159 (0.116 , 0.209)
810	37	6	0.133 (0.094 , 0.18)
900	31	5	0.112 (0.076 , 0.156)
990	26	1	0.108 (0.072 , 0.151)
1080	25	2	0.099 (0.065 , 0.141)
1170	23	4	0.082

Base CD4 500+			
			(0.051 , 0.121)
1260	19	5	0.06 (0.035 , 0.096)
1350	14	3	0.047 (0.025 , 0.08)
1440	11	3	0.034 (0.016 , 0.064)
1530	8	3	0.022 (0.008 , 0.047)
1710	5	1	0.017 (0.006 , 0.041)
1800	4	1	0.013 (0.004 , 0.035)

Table 10 indicates that this last group has the healthiest level of patients in the cohort. The estimated survival function is slightly better than the previous level, however, there is still much overlapping in confidence intervals.

4. Survival Analysis by Service Community

Here survival functions are estimated for each service separately. Service is another time-independent variable, so no increase in the number at risk is present.

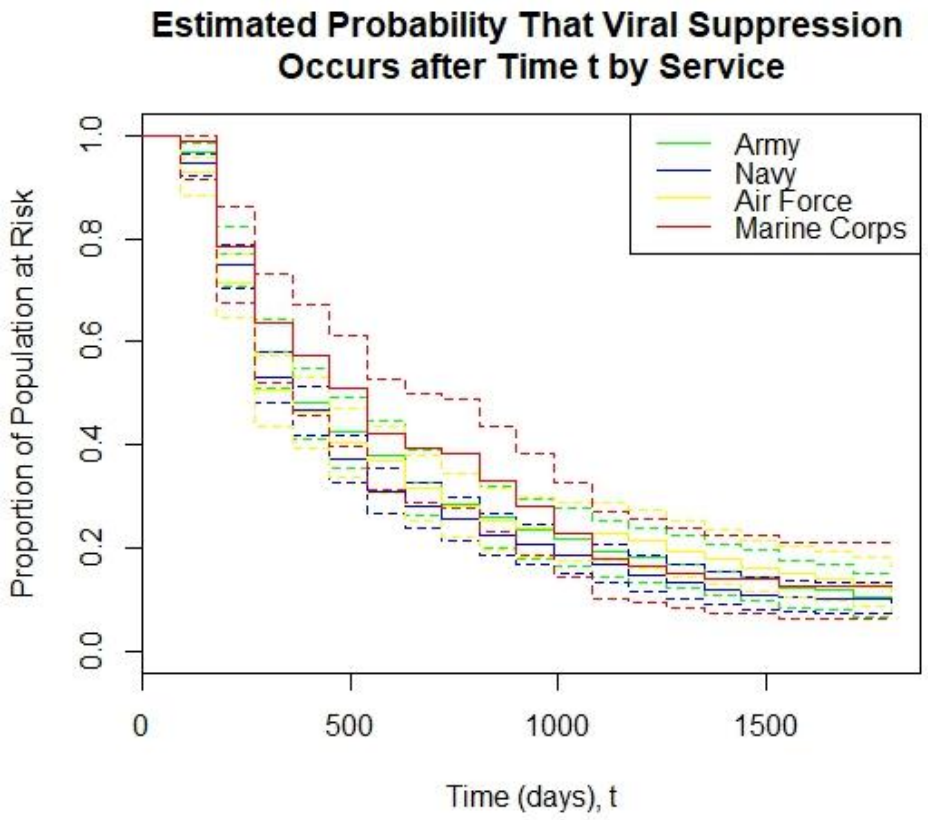


Figure 14. Estimated Survival Function of Viral Suppression Times by Service Affiliation with 95% Confidence Intervals (Dotted Lines)

In this case, Figure 14 is not as visually informative as some of its counterparts. There is significant overlapping of the survival function estimates between services as time progresses, and no survival function estimate stochastically dominates any other. Confidence bounds overlap for much of the observed time.

Table 11. Estimated Survival Function of Army Patients

Army			
t	n.risk	n.event	$\hat{S}(t)$
90	204	7	0.966 (0.929 , 0.983)
180	197	40	0.77 (0.706 , 0.822)
270	158	39	0.58 (0.509 , 0.644)
360	120	20	0.483

Army			
t	n.risk	n.event	$\hat{S}(t)$
			(0.413 , 0.549)
450	99	12	0.424 (0.356 , 0.491)
540	87	9	0.381 (0.314 , 0.446)
630	78	11	0.327 (0.264 , 0.391)
720	68	9	0.284 (0.224 , 0.346)
810	59	5	0.260 (0.202 , 0.321)
900	53	5	0.235 (0.18 , 0.295)
990	47	3	0.22 (0.166 , 0.279)
1080	44	5	0.195 (0.144 , 0.252)
1170	39	2	0.185 (0.135 , 0.241)
1260	37	3	0.170 (0.122 , 0.225)
1350	34	3	0.155 (0.109 , 0.208)
1440	31	2	0.145 (0.101 , 0.197)
1530	29	4	0.125 (0.084 , 0.175)
1620	25	1	0.12 (0.08 , 0.169)
1710	24	3	0.105 (0.068 , 0.152)
1800	21	1	0.100 (0.064 , 0.146)

In Table 11, the Army cohort, the estimated survival function progresses steadily downwards, ending up very close to 10%. The cohort experiences the largest drops in survival function estimates in the first 4 time periods, losing over 50% of the at risk group in this time, while only about 40% drop over the rest of the time period.

Table 12. Estimated Survival Function of Navy Patients

Navy			
t	n.risk	n.event	$\hat{S}(t)$
90	415	22	0.947 (0.921 , 0.965)
180	393	82	0.749 (0.705 , 0.788)
270	314	91	0.532 (0.483 , 0.579)
360	222	27	0.468 (0.419 , 0.514)
450	195	39	0.374 (0.328 , 0.42)
540	156	26	0.312 (0.268 , 0.356)
630	129	12	0.283 (0.24 , 0.326)
720	118	11	0.256 (0.215 , 0.299)
810	106	12	0.227 (0.188 , 0.269)
900	94	8	0.208 (0.17 , 0.248)
990	86	8	0.189 (0.153 , 0.228)
1080	78	8	0.169 (0.135 , 0.207)
1170	70	8	0.15 (0.118 , 0.186)
1260	62	7	0.133 (0.102 , 0.168)
1350	55	5	0.121 (0.092 , 0.154)
1440	50	4	0.111 (0.083 , 0.144)
1530	46	2	0.106 (0.079 , 0.138)
1620	44	2	0.102 (0.075 , 0.133)
1800	42	2	0.097 (0.071 , 0.128)

Table 12 shows Navy patients also reach about 90% chance of viral suppression, but confidence intervals overlap with those of the Army patients.

Table 13. Estimated Survival Function of Air Force Patients

Air Force			
t	n.risk	n.event	$\hat{S}(t)$
90	206	15	0.927 (0.882 , 0.955)
180	191	44	0.714 (0.647 , 0.77)
270	149	43	0.508 (0.438 , 0.573)
360	104	9	0.464 (0.395 , 0.53)
450	95	12	0.405 (0.338 , 0.471)
540	83	7	0.371 (0.305 , 0.436)
630	76	11	0.317 (0.255 , 0.381)
720	65	7	0.283 (0.223 , 0.346)
810	59	6	0.254 (0.197 , 0.315)
900	52	3	0.24 (0.184 , 0.3)
990	49	2	0.23 (0.175 , 0.289)
1170	47	3	0.215 (0.162 , 0.274)
1260	44	4	0.196 (0.145 , 0.252)
1350	40	3	0.181 (0.132 , 0.236)
1440	37	4	0.161 (0.115 , 0.215)
1530	33	2	0.152 (0.107 , 0.204)
1620	31	2	0.142 (0.098 , 0.193)
1710	29	2	0.132 (0.09 , 0.182)
1800	27	3	0.117 (0.078 , 0.166)

Table 13 shows that the estimated survival function in the Air Force cohort decreases slightly faster in times 1-4 than Army and Navy; however, there is again much overlapping of confidence intervals, and the Air Force also ends up with around 90% chance of viral suppression.

Table 14. Estimated Survival Function of Marine Corps Patients

Marines			
t	n.risk	n.event	$\hat{S}(t)$
90	79	1	0.987 (0.914 , 0.998)
180	78	16	0.785 (0.677 , 0.86)
270	63	12	0.635 (0.52 , 0.73)
360	51	5	0.573 (0.457 , 0.673)
450	46	5	0.511 (0.397 , 0.614)
540	40	7	0.421 (0.312 , 0.527)
630	33	2	0.396 (0.289 , 0.501)
720	31	1	0.383 (0.277 , 0.488)
810	30	4	0.332 (0.231 , 0.436)
900	26	4	0.281 (0.187 , 0.382)
990	22	4	0.23 (0.144 , 0.327)
1080	18	4	0.179 (0.104 , 0.27)
1170	14	1	0.166 (0.094 , 0.256)
1260	13	1	0.153 (0.084 , 0.241)
1350	12	1	0.14 (0.075 , 0.226)
1530	11	1	0.128 (0.066 , 0.211)

In Table 14, the Marine Corps cohort, likelihood of viral suppression is much like the others. However, the Marine Corps estimated survival function is relatively higher throughout the majority of the observed time frame. Confidence intervals are much wider due to small sample size, and there is a surprising drop toward the end of the time frame, where the Marine Corps catches up to the rest of the cohorts.

5. Survival Analysis by Number of PCS

Next, survival functions were estimated as a function of number of PCS. Values of PCS ranged from zero, staying in the same location for all 5 years, to 4, moving 4 times during the 5-year cascade of treatment. However, because there are so few patients with more than one move, we combined them into a single group of one or more moves (PCS = 1+). This is another time-dependent variable, like treatment. Patients who move at least once during treatment switch over to the PCS = 1+ cohort after their move. As such, the number of at risk for PCS = 1+ can increase.

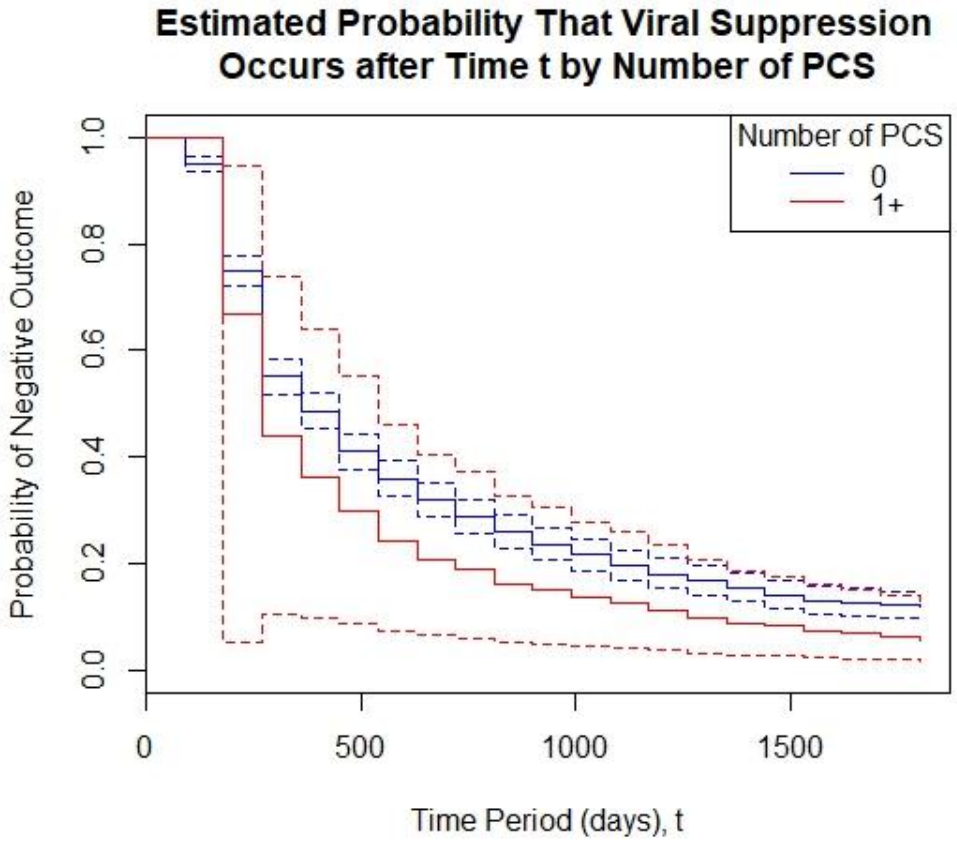


Figure 15. Estimated Survival Function of Viral Suppression Times by Number of PCS with 95% Confidence Intervals (Dotted Lines)

The trends shown in Figure 15 show very little difference between those who moved and those who did not. While it may appear that those who move fare better, the uncertainty in this measurement is so large that its confidence bounds encompass the estimated survival function of those who did not move.

Table 15. Estimated Survival Function of Patients with No Moves

PCS = 0			
t	n.risk	n.event	$\hat{S}(t)$
90	904	45	0.95 (0.934 , 0.963)
180	856	181	0.749 (0.72 , 0.776)
270	634	168	0.551 (0.517 , 0.583)
360	452	53	0.486 (0.452 , 0.519)
450	382	59	0.411 (0.378 , 0.444)
540	313	39	0.36 (0.327 , 0.393)
630	261	28	0.321 (0.289 , 0.354)
720	227	23	0.289 (0.258 , 0.321)
810	195	19	0.261 (0.23 , 0.292)
900	171	16	0.236 (0.207 , 0.267)
990	150	12	0.217 (0.188 , 0.248)
1080	136	13	0.197 (0.169 , 0.226)
1170	118	9	0.182 (0.154 , 0.211)
1260	106	8	0.168 (0.141 , 0.197)
1350	96	7	0.156 (0.13 , 0.184)
1440	86	8	0.141 (0.116 , 0.169)
1530	78	5	0.132 (0.108 , 0.159)
1620	71	2	0.128 (0.104 , 0.155)
1710	69	3	0.123 (0.099 , 0.149)
1800	65	2	0.119 (0.095 , 0.145)

In Table 15, those patients who did not move reached about 90% chance of viral suppression by the end of the observed time.

Table 16. Estimated Survival Function l of Patients with 1 Move or More

PCS = 1+			
t	n.risk	n.event	$\hat{S}(t)$
180	3	1	0.667 (0.054 , 0.945)
270	50	17	0.44 (0.106 , 0.74)
360	45	8	0.362 (0.099 , 0.64)
450	53	9	0.3 (0.088 , 0.551)
540	53	10	0.244 (0.075 , 0.463)
630	55	8	0.208 (0.066 , 0.404)
720	55	5	0.189 (0.061 , 0.372)
810	59	8	0.164 (0.053 , 0.327)
900	54	4	0.152 (0.05 , 0.305)
990	54	5	0.138 (0.046 , 0.28)
1080	51	4	0.127 (0.042 , 0.26)
1170	52	5	0.115 (0.038 , 0.237)
1260	50	7	0.099 (0.033 , 0.207)
1350	45	5	0.088 (0.03 , 0.186)
1440	43	2	0.084 (0.028 , 0.178)
1530	41	4	0.075 (0.025 , 0.162)
1620	39	3	0.07 (0.023 , 0.151)
1710	36	2	0.066 (0.022 , 0.143)
1800	35	4	0.058 (0.02 , 0.128)

Table 16 shows much the same results as in Table 15. The chance of viral suppression is almost identical, at t = 20 (1800 days).

B. MODEL FORMULATION

In this section, we fit several Cox proportional hazards models to study the combined effects of several factors on the survival function.

1. Model Fitting

We were unable to fit a single proportional hazards model using all variables. Several levels of categorical variables were collapsed due to small sample size. In the rank variable, warrant officers were combined with officers, because very few warrant officers appear in the data. In the race category, all non-white races were combined into one category, and in the PCS category, number of PCS one or more were combined together. Next, non-proportionality was accounted for by adding interaction terms to the model. Interactions included age group with number of PCS, treatment with time, time treated with treatment group, and treatment group with time, and PCS with time. Once the model met proportional hazards assumptions, using backward elimination, all variables that were nonsignificant to the regression were removed. Some variables were highly correlated to others, so one of them could be removed, such as age, since age group already appeared in the model, and ADHERE_95 and ADHERE, because they were strongly correlated to the remaining ADHERE_90 variable. Gender was also removed from the model, as females account for a small proportion of the data. The final model met proportional hazards assumptions globally (p value = 0.965, using Granbsch and Therneau (1994) test for proportional hazards), and contained 4 variables: rank, treatment, baseline CD4, and treatment group. Treatment and treatment group retained their time interactions in the final model.

2. Interpretation of the Model Coefficients

Once the final model was fit, the Cox proportional hazards coefficients could be interpreted. All coefficients for categorical variables are either calculated with reference to the base level of a category, or arbitrarily related to the first level for categorical variables. The exponential of the coefficient, θ, gives the percent increase or decrease in the likelihood of attaining viral suppression, with reference to the base level of the factor.

This means variables with θ greater than 1 show patients with that corresponding trait are more likely to reach viral suppression sooner than the baseline. Conversely, variables with θ less than 1 indicate patients with that trait are less likely to reach viral suppression as soon the baseline, so that trait corresponds to a negative outcome for the patient.

This model gives a pseudo- R-squared value of 0.242, which is defined as the improvement in the model from the null model, where all θ are set to one (Fox and Weisberg 2011). Table 17 gives $\hat{\theta}$, estimates of θ, and approximate 95% confidence intervals (CI) for θ, where REF indicates the level of the categorical variable for which θ is defined to be 1.

Table 17. Cox Proportional Hazards Coefficients of the Model

	$\hat{\theta}$	Lower 95% CI for θ	Upper 95% CI for θ
Rank: Officer	REF	REF	REF
Rank: Enlisted	0.765	0.636	0.920
Rank: N/A	1.572	0.996	2.482
Untreated	REF	REF	REF
Treated	10.076	3.623	28.024
Base CD4 < 200	REF	REF	REF
Base CD4 200 - 350	0.922	0.721	1.180
Base CD4 350 - 500	0.888	0.693	1.138
Base CD4 > 500	1.171	0.916	1.497
Treat if CD4 < 200	REF	REF	REF
Treat if CD4 < 350	1.797	1.394	2.317
Treat if CD4 < 500	1.789	0.712	4.490

In Table 17, enlisted personnel did significantly worse than officers (p value = 0.004), and were about 25% less likely to reach viral suppression than officers were. Those without an applicable rank did slightly better than officers (p value = 0.052) and were about 60% more likely to reach viral suppression. Being treated increased an individual's chances of viral suppression significantly (p value = 0.000). Having a baseline CD4 between 200 and 349 did not significantly increase an individual's chance of viral suppression compared to those with baseline CD4 less than 200 (p value =

0.520). Those with a baseline CD4 between 350 and 500 were also not significantly different (p value = 0.349). Those individuals who had a baseline CD4 above 500 were almost 30% more likely to reach viral suppression than those with a baseline CD4 less than 200 ($\hat{\theta}$ = 1.172, C.I. (0.916 , 1.497)). Those in the medium inclusive treatment policy were 80% more likely to reach viral suppression than the most restrictive policy (p value = 0.000). Those in the least restrictive policy did as well, being almost 80% more likely to reach viral suppression than the most restrictive policy, but this improvement was not significant at the 5% level of significance.

C. ATTAINMENT OF 90-90-90

With the variable of viral suppression available in the final dataset, it was possible to determine, of the study population treated, how many of them reached viral suppression. As such, the dataset was partitioned to only include treated individuals. One minus the Kaplan-Meier survival function estimate was used for this cohort, to estimate the cumulative distribution function (CDF) for viral suppression time among those who were treated.

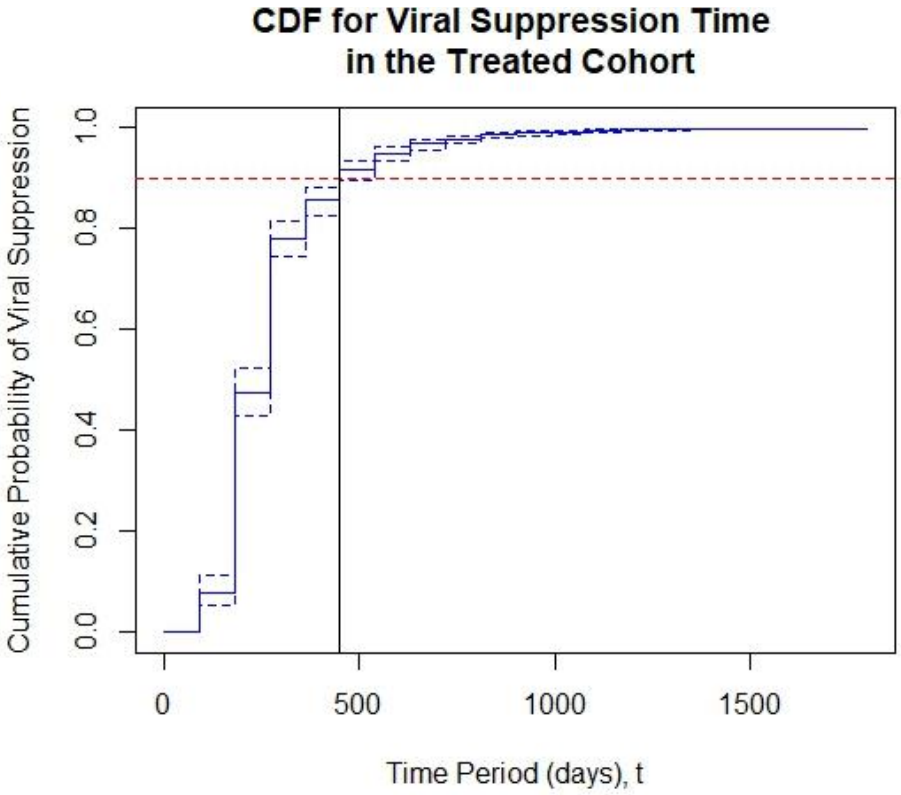
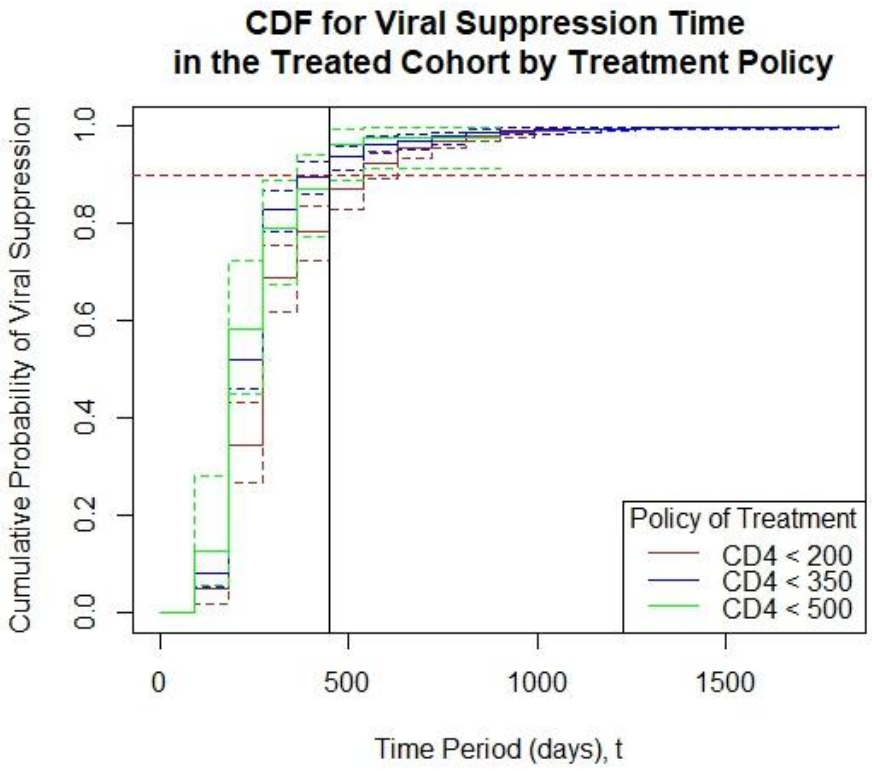


Figure 16. Estimated CDF for Viral Suppression Time in Treated Cohort

From Figure 16, we see that overall, without even taking into account time, changes in treatment guidelines, or the other factors in this analysis, the treated military cohort achieved about an estimated 99% cumulative probability of viral suppression in this 5-year study window. The CDF of the treated cohort's time to reach viral suppression passed 90% at t = 5 (450 days).

1. 90-90-90 by Treatment Group

The next goal was to take a closer look at how effective the previous treatment policies truly were at helping patients reach viral suppression effectively.



Vertical line corresponds to time the non-partitioned cohort achieved 90% cumulative probability of viral suppression.

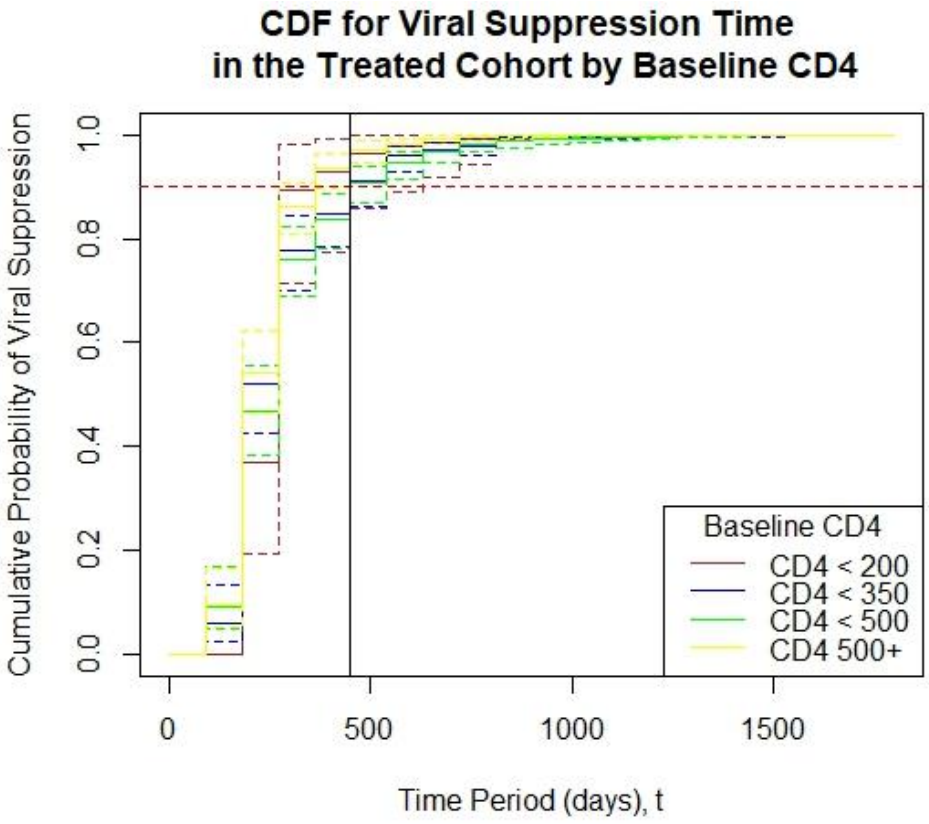
Figure 17. Estimated CDF for Viral Suppression Time Suppression in Treated Cohort, by Treatment Policy

In Figure 17, all treated cohorts CDFs reach 90% probability of viral suppression around the same time. Their confidence bands overlap within the time interval of the overall cohort. The mean time to reach viral suppression in the first treatment policy is estimated to be 313 days, with a standard error of 13.14 days. The second cohort reached viral suppression with an estimated mean of about 258 days, with a standard error of 8.87, while the most inclusive treatment policy reached viral suppression with an estimated mean of about 270 days with a standard error of 35.08 days.

2. 90-90-90 by Base CD4

Directly related to treatment policy, of those individuals whose baseline CD4 was 500 or greater, the CDF of time to reach viral suppression reached 90% sooner than those in the next-healthiest treatment group (Figure 18). This once again suggests that more inclusive treatment programs that begin ART sooner in patients, regardless of the

relative health of the patient, have much better results, and can aid in reaching 90-90-90 sooner.



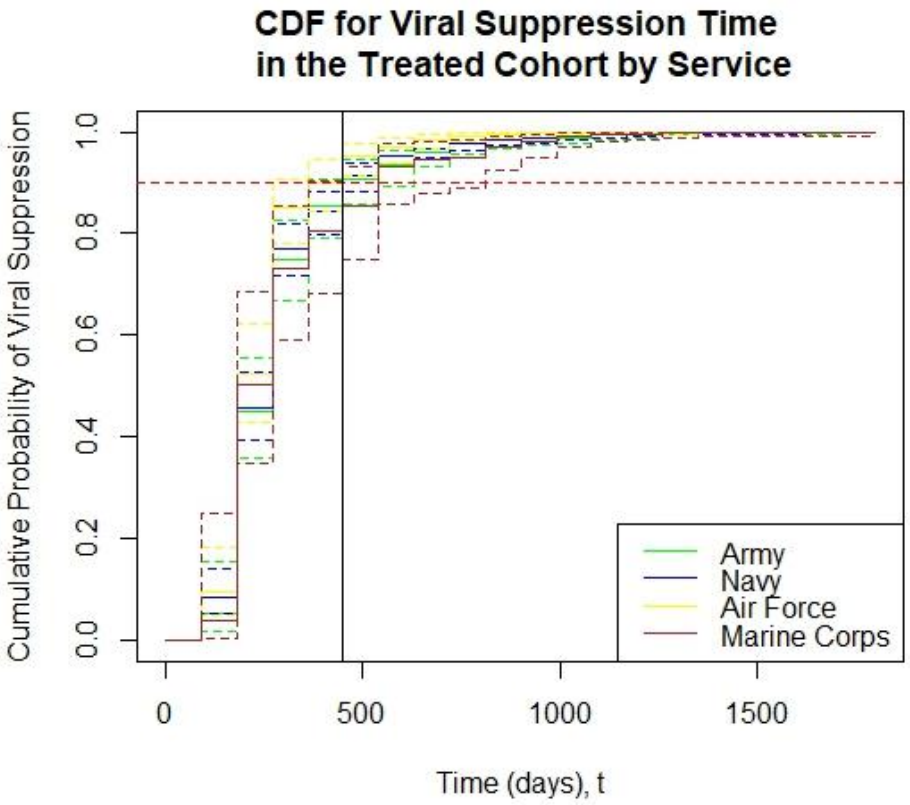
Vertical line corresponds to the time at which the non-partitioned cohort reached 90% cumulative probability of viral suppression.

Figure 18. Estimated CDF for Viral Suppression Time Suppression in Treated Cohort, by Baseline CD4 Count

In Figure 18, the largest difference in CDF of time to reach viral suppression is between the healthiest and second-healthiest patients. The mean time to reach viral suppression of those with baseline CD4 greater than 500 is estimated to be 237 days, with a standard error of 8.5 days. The second healthiest cohort, with baseline CD4 between 350 and 500, reached viral suppression with an estimated mean of 278 days, with a standard error of 13.1 days.

3. 90-90-90 by Service

Regarding the differences in service affiliation: there were no appreciable differences between the services in CDFs of time to reach viral suppression.



Vertical line corresponds to the time at which the non-partitioned cohort reached 90% cumulative probability of viral suppression.

Figure 19. Estimated CDF for Viral Suppression Time Suppression in Treated Cohort, by Service

In the Figure 19, all treated cohorts of each service have a CDF which reaches 90% probability of viral suppression around the non-partitioned cohort's time of 450 days. The shortest estimated mean time to reach viral suppression was found in the Air Force, 247 days with a standard error of 11.9. The longest mean estimated time to reach viral suppression was in the Marine Corps, at 298 days with a standard error of 29.5.

V. CONCLUSIONS

A. INITIAL SURVIVAL ANALYSIS

As shown in Figure 16, the military surpasses 90% cumulative probability of reaching viral suppression, thus meeting all three targets of 90-90-90. That treatment has a significant impact on the outcome of the patient is a very expected result. From Figure 11, it is readily apparent that treatment is essential to reaching viral suppression. Those who engage in ART are much more likely to reach this positive outcome. However, a closer look at the rest of the factors in this analysis may shed some light on less obvious results.

1. Treatment Group

In this survival analysis, visualized in Figure 12, the two least restrictive policies showed decreased probability of remaining non-virally suppressed, while the most restrictive group fared much worse. Those patients who were treated when their CD4 was 500 or less fared much better than those who waited to be treated until their CD4 fell below 350 or 200. More inclusive treatment policies mean patients are more likely to have a positive outcome. Treating patients regardless of their relative immune system strength is a proactive approach which should show better results than previous reactive approaches, allowing patients to reach viral suppression much sooner. Figure 17 shows that there is not necessarily a perfectly distinguishable relationship between the policies, as they all reach 90% cumulative probability of viral suppression around the same time. However, the most inclusive treatment policy (treating patients with CD4 < 500) tends to reach it first. This is corroborated by international policy, as UNAIDS has stated, "Countries will need to align national treatment guidelines with evidence documenting the clear benefits of early treatment initiation" (UNAIDS 2014). This cohort confirms the necessity and benefits of early treatment initiation, regardless of relative patient health.

2. Baseline CD4

Similarly, those with higher CD4 levels in Figure 13 upon starting treatment tend toward viral suppression sooner than those who had lower CD4 levels. However, in Figure 18, time to 90% cumulative probability of viral suppression did not display much difference by baseline CD4. Increases in baseline CD4 still display decreases in time to viral suppression. This concurs with UNAIDS previously mentioned statement, that earlier initiation of ART drives progress toward viral suppression.

3. Service Community

Service community was not strictly relevant in the survival analysis, and most pairwise comparisons between the services were non-significant. The only comparison of note was that, on average, the Air Force reached 90% cumulative probability of viral suppression sooner, while the Marine Corps reached it later. The lack of strong differences between the services agrees with the fact that each service follows the same standards of care as released by the NIH.

B. COX PROPORTIONAL HAZARDS MODEL

While the Kaplan-Meier model was informative for survival rates between different levels of a factor, the Cox proportional hazards model can inform how combinations of factors are important to reaching viral suppression.

1. Rank

With respect to officers, with all other factors held constant, enlisted personnel fare significantly worse in this cohort. Enlisted were 25% less likely to reach viral suppression than officers were. Other factors may be at work here, rather than just rank disparity, such as risk behaviors, age differences, adherence, and other demographics, but such interactions are outside the scope of this analysis.

2. Treatment

As already established in the initial survival analysis, individuals who are treated do significantly better than those who are not. Even with all other factors the same, those

individuals who are treated are 10 times more likely to reach viral suppression than if they are untreated. These results agree with UNAIDS policy, which says "the most substantial [health and economic] benefits occur when treatment is available to all people living with HIV, regardless of CD4 count" (UNAIDS 2014).

3. Baseline CD4

With all other factors held constant, compared to the factor level CD4 < 200, increasing baseline CD4 to 350, and even 499 has little effect on risk. However, once CD4 increases above 500, while not significant at the 95% confidence level in the observed time period, individuals are almost 20% more likely to reach viral suppression than those whose CD4 is less than 200 at treatment initiation. As stated previously, UNAIDS has stressed the importance of initiation of treatment regardless of CD4 count.

4. Treatment Group

A steady increase in likelihood of viral suppression can be seen as treatment groups become more inclusive. This coincides with the discussion of baseline CD4, as UNAIDS has repeatedly said early initiation of ART is key to reaching viral suppression. Policies which allow more patients, and healthier patients, to begin treatment early give those patients the best chance of reaching good health.

C. FUTURE WORK

While the above-mentioned models have provided some useful insights into the factors that affect the health of this cohort, some areas can be improved upon or better informed with future studies and more rigorous analysis.

1. Patient Follow-Up and Data Processing

An area of improvement on this model is finding a way to deal with the patients who do not have data for a given time frame, but reappear in the cohort later. Currently, if a patient does not have data for a time period, but enters viral suppression in the next, the assumption is that they did not reach viral suppression in the previous time period. As such, these estimates may be biased toward worse patient performance than what actually

occurs. However, without knowledge of these time intervals, assumptions must be made to correctly use these survival analysis tools.

2. Factors of Interest

The rank factor could be looked at more closely to determine exactly how such a factor plays such a significant role in the final model. Interactions with risk behaviors and age groups could be considered, as well as analysis of the PCS schedule and adherence differences between the groups. Lastly, expanding the data from the current 904 individuals to include a larger portion of the cohort would be informative. However, it would change processing of variables such as treatment group, as older or newer data are introduced to the set.

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